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# CONTENTS OF VOL. 218

## ORIGINAL ARTICLES

### No. 1—JULY

- Studies of the Effects of Flavonoids on Roentgen Irradiation Disease. I. Protective Influence of Rutin in Irradiated Dogs. By JOHN B. FIELD, PH.D., M.D., and PAUL E. REKERS, M.D., Rochester, New York . . . . . 1
- Evidence on the Genesis of Certain Common Nasal Disorders. By THOMAS H. HOLMES, M.D., HELEN GOODELL, A.B., STEWART WOLF, M.D., and HAROLD G. WOLFF, M.D., New York, New York . . . . . 16
- Serial Determinations of Prothrombin Activity in Pregnancy and the Puerperium. By ERNEST COTLOVE, M.D., DAVID SPIRO, M.D., and JEFFERSON J. VORZIMER, M.D., New York, New York . . . . . 28
- Anomalous Right Pulmonary Vein Entering the Inferior Vena Cava: Two Cases Diagnosed During Life by Angiocardiography and Cardiac Catheterization. By CHARLES T. DOTTER, M.D., NORRIS M. HARDISTY, CAPT. (MC), USN, and ISRAEL STEINBERG, M.D., New York, New York . . . . . 31
- Clinical Evaluation of Direct Writing Electrocardiography. By WARREN J. HUNZICKER, M.D., and HAROLD D. LEVINE, M.D., Boston, Massachusetts . . . . . 37
- The Coagulation Time of Blood in Silicone Tubes. By HAROLD MARGULIES, M.D., and NELSON W. BARKER, M.D., Rochester, Minnesota . . . . . 42
- The Coagulation Time of Blood in Silicone Tubes in Patients Receiving Dicumarol. By HAROLD MARGULIES, M.D., and NELSON W. BARKER, M.D., Rochester, Minnesota . . . . . 52
- A Hematologic and Electrophoretic Study on Blood Regeneration in Dogs Subjected to Repeated Phlebotomy. By CHARLES W. MUSHETT, PH.D., KURT G. STERN, PH.D., and ROBERT H. SILBER, PH.D., Rahway, New Jersey, and Brooklyn, New York . . . . . 58
- The Direction of the Precordial T Wave in 321 Normal Infants and Children. By LAWRENCE KUSKIN, M.D., and LOUIS BROCKMAN, M.D., Brooklyn, New York . . . . . 65
- Naturally-Occurring Anticoagulants and Accelerator Substance in Human Blood. By FRED J. SCHILLING, M.D., and ALBERT DE NATALE, PH.D., New York, New York . . . . . 70
- Continuous Peritoneal Irrigation in the Treatment of Intractable Edema of Cardiac Origin. By SAMUEL J. SCHNEIERSON, M.D., New York, New York . . . . . 76
- Studies of a Sulfadiazine-Sulfamerazine Combination with Special Reference to Treatment of Pneumonia. By PAUL D. SHORE, M.D., HARRISON F. FLIPPIN, M.D., and JOHN G. REINHOLD, PH.D., Philadelphia, Pennsylvania . . . . . 80

### No. 2—AUGUST

- The Absorption of Gold from Pellets of Gold Salts (Aurothioglycolanilide) Implanted Subcutaneously and Intramuscularly. By H. H. MARGOLIS, M.D., GEORGE H. FETTERMAN, M.D., and PAUL S. CAPLAN, M.D., Pittsburgh, Pennsylvania . . . . . 121
- The Treatment of Pneumonia and Other Infections With a Soluble Sulfonamide. Gantrosan (NU-445; 3, 4-Dimethyl-5-Sulfanilamido-Isoxazole). By ROBERT L. BRUCKHOUSE, M.D., MARK H. LEPPER, M.D., THOMAS E. STONE, M.D., and HARRY F. DOWLING, M.D., Washington, D. C. . . . . 153

|  |     |
|--|-----|
| The Treatment of Gonorrheal Arthritis With Penicillin. By NORMAN SPITZER, M.D., and OTTO STEINBROCKER, M.D., New York, New York . . . . .  | 138 |
| Inefficacy of Prophylactic Streptomycin in an Outbreak of Salmonella Gastro-Enteritis. By J. J. ROWLAND REID, M.D., DANIEL E. JENKINS, M.D., and CORA RUST OWEN, Ph.D., Ann Arbor, Michigan . . . . .  | 145 |
| Multiple Myeloma Associated With Polycythemia. By JOHN H. LAWRENCE, M.D., and ROBERT L. ROSENTHAL, M.D., Berkeley, California . . . . .  | 149 |
| Venous Thrombo-Embolic Phenomena. By ALBERT W. COOK, LT. (J.G.) M.C., U.S.N.R., and HAROLD A. LYONS, COMMANDER, M.C., U.S.N., St. Albans, New York . . . .   | 155 |
| Experiences With 116 Juvenile Campers in a New Summer Camp for Diabetic Boys. By A. J. GABRIELE, M.D., and ALEXANDER MARBLE, M.D., Boston, Massachusetts . .   | 161 |
| Insulin Fat Atrophy. By D. L. OESTREICHER, M.D., and E. M. WATSON, M.D., London, Canada . . . . .  | 172 |
| Pernicious Anemia Complicated by Syphilis. By SIMON ZIVIN, M.D., and GEORGE V. LEROY, M.D., Chicago, Illinois . . . . .  | 179 |
| Premature Calcification of the Costal Cartilages: Its Frequent Association With Symptoms of Non-Organic Origin. By JOHN L. HORNER, M.D., St. Louis, Missouri . .   | 186 |
| The Value of Liver Function Tests in General Hospital Practice. By CAMPBELL MOSES, M.D., Pittsburgh, Pennsylvania . . . . .  | 194 |
| Studies in Pernicious Anemia Patients Treated with Liver Extract and Folic Acid Antagonists. By LEO M. MEYER, M.D., NORTON D. RITZ, M.D., ANTHONY CACCесе, M.D., JULIUS RUTZKY, M.D., ARTHUR SAWITSKY, M.D., and GEORGE BOCK, M.D., New York, New York . . . . . | 197 |
| The Pain Reaction Threshold in the Menopausal Syndrome. By ROBERT F. SCHILLING, M.D., and MARC J. MUSSER, M.D., Madison, Wisconsin . . . . .   | 204 |
| Pain Reaction Thresholds in Patients With Peptic Ulcer. By ROBERT F. SCHILLING, M.D., and MARC J. MUSSER, M.D., Madison, Wisconsin . . . . .   | 207 |
| Recurrent Migrainoid Headaches Associated With Spontaneous Hypoglycemia. By CHAS. F. WILKINSON, JR., M.D., Battle Creek, Michigan . . . . .  | 209 |

## No. 3—SEPTEMBER

|   |     |
|---|-----|
| Metastases in Bone Marrow and Myelophthisic Anemia from Carcinoma of the Prostate. By R. W. RUNDLES, M.D., and U. JONSSON, M.D., Durham, North Carolina . . . .   | 241 |
| The Pituitary Gland of Rats with Experimental Goiter. By GEORGE C. HENEGAR, M.D., and GEORGE M. HIGGINS, Ph.D., Rochester, Minnesota . . . . .  | 251 |
| The Treatment of Pneumococcic Meningitis with Penicillin. By EMANUEL APPELBAUM, M.D., JACK NELSON, M.D., and MICHAEL B. ALBIN, M.D., New York, New York . .   | 260 |
| The Chemical Combination of Insulin with Muscle (Diaphragm) of Normal Rat. By WILLIAM C. STADIE, M.D., NIELS HAUGAARD, Ph.D., JULIAN B. MARSH, M.D., and A. GORMAN HILLS, M.D., Philadelphia, Pennsylvania . . . . .            | 265 |
| Hormonal Influences on the Chemical Combination of Insulin with Rat Muscle (Diaphragm). By WILLIAM C. STADIE, M.D., NIELS HAUGAARD, Ph.D., A. GORMAN HILLS, M.D., and JULIAN B. MARSH, M.D., Philadelphia, Pennsylvania . . . . | 275 |
| The Effect of Body Position and Reference Level on the Determination of Venous and Right Auricular Pressure. By JAMES O. DAVIS, Ph.D., M.D., and NATHAN W. SHOCK, Ph.D., Baltimore, Maryland . . . . .                          | 281 |

|  |     |
|--|-----|
| Renal Studies in Acute Infectious (Epidemic) Hepatitis. By JOHN D. FARQUHAR, M.D., Philadelphia, Pennsylvania . . . . .  | 291 |
| Clinical Report on the Toxicity of a New Mercurial Diuretic (Thiomerin) for Subcutaneous Administration. By ALAN R. FEINBERG, M.D., JULIEN H. ISAACS, M.D., and WILLIAM S. BOIKAN, M.D., Chicago, Illinois . . . . .                           | 298 |
| The Toxicity of Intravenous Ammonium Compounds. By NORMAN W. KARR, Ph.D., M.D., and EDWARD L. HENDRICKS, M.S., Portland, Oregon . . . . .  | 302 |
| Alterations in the Serum Potassium and Their Relation to Certain Constituents of the Blood in Diabetic Acidosis. By CARL S. NADLER, M.D., SAMUEL BELLET, M.D., JOHN G. REINHOLD, Ph.D., and MARY LANNING, Philadelphia, Pennsylvania . . . . . | 308 |
| The Increased Hypoprothrombinemic Effect of a Small Dose of Dicumarol in Congestive Heart Failure. By DANIEL STATS, M.D., and SELVAN DAVISON, M.D., New York, New York . . . . .   | 318 |

## No. 4—OCTOBER

|  |     |
|--|-----|
| A Study of Factors Affecting the Prognosis of Cerebral Vascular Accident. By E. C. TENNENT, M.D., and J. W. HARMAN, M.B., Madison, Wisconsin . . . . .   | 361 |
| Major Etiological Factors Producing Delayed Resolution in Pneumonia. By THEODORE K. GLEICHMAN, M.D., MAX M. LEDER, M.D., and DANIEL W. ZAHN, M.D., Fort Logan, Colorado . . . . .                            | 369 |
| The Treatment of Falciparum Malaria with Intramuscular Chloroquine. By CHARLES G. SPICKNALL, M.D., LUTHER L. TERRY, M.D., and G. ROBERT COATNEY, Ph.D., Bethesda, Maryland . . . . .                         | 374 |
| Localized Sealed-Off Perforation in Recurrent Duodenal Ulcer. By MAURICE FELDMAN, M.D., Baltimore, Maryland . . . . .  | 378 |
| Co-Existent Hodgkin's Disease and Kaposi's Sarcoma. By RAPHAEL H. GREENSTEIN, M.D., and ALFRED S. CONSTON, M.D., Philadelphia, Pennsylvania . . . . .  | 384 |
| The Murmurs of Cardiac Aneurysm. By DAVID SCHERF, M.D., and ALAN M. BROOKS, M.D., New York, New York . . . . .   | 389 |
| Congenital Polycystic Disease of the Kidney: Review of the Literature, and Data on 207 Cases By J. E. RALL, M.D., and HOWARD M. ODEL, M.D., Rochester, Minnesota . . . . .                                   | 399 |
| Diabetic Nephropathy. By EUGENE I. ZINS, M.D., New York, New York . . . . .  | 408 |
| Albuminuria in Service Recruits: A Laboratory Study of 193 Cases Referred From Routine Medical Examination. By HAROLD B. SALT, M.Sc., and WILLIAM H. McMENEMEY, D.M., Worcester, England . . . . .           | 419 |
| Acronecrosis Due to Fibrin Thrombi and Endothelial Cell Thrombi. By WALTER PAGEL, London, England . . . . .  | 425 |
| The Administration of Histamine During Pregnancy: Apparent Lack of a Clinical Oxytocic Effect with Small Doses. By THOMAS W. McELIN, M.D., and BAYARD T. HORTON, M.D., Rochester, Minnesota . . . . .        | 432 |
| The Absorption, Distribution, Excretion and Toxicity of Bacitracin in Man. By HAROLD A. ZINTEL, M.D., RONALD A. MA, M.D., ANNA C. NICHOLS, M.S., and HELEN ELLIS, B.A., Philadelphia, Pennsylvania . . . . . | 439 |

## No. 5—NOVEMBER

|   |     |
|---|-----|
| Blood Temperature and Its Control. By H. C. BAZETT, M.D., Philadelphia, Pennsylvania . . . . .  | 453 |
| Exophthalmic Goiter in Children: Treatment With Propylthiouracil. By ARNOLD S. JACKSON, M.D., and HAROLD B. HALEY, M.D., Madison, Wisconsin . . . . . | 493 |

|  |     |
|--|-----|
| Liver and Kidney Function in Rocky Mountain Spotted Fever. By WILLIAM A. WOLFF, PH.D., and GEORGE T. HARRELL, M.D., Winston-Salem, North Carolina . . . . .  | 500 |
| Embolization With Material From Atheromata. By FREDERICK G. ZAK, M.D., and KURT ELIAS, M.D., New York, New York . . . . .  | 510 |
| The Occurrence of Chronic Cyanosis in Cases of Atrial Septal Defect, By ARTHUR SELZER, M.D., and ALVIN E. LEWIS, M.D., San Francisco, California . . . . .   | 516 |
| A Study of 22 Cases of Carrion's Disease With Intercurrent Malaria, By WILLIAM E. RICKETTS, M.D., Chicago, Illinois . . . . .  | 525 |
| Metabolic Study of Gynecomastia Associated With Liver Disease. By EUGENE L. COODLEY, M.D., and WILLIAM E. MOLLE, M.D., Los Angeles, California . . . . .   | 531 |
| Liver Function in Diabetes Mellitus. By HAROLD BROWN, M.D., Salt Lake City, Utah . . . . .   | 540 |
| The Influence of Physical Therapy Procedures on the Intra-Articular Temperature of Normal and Arthritic Subjects. By JOSEPH L. HOLLANDER, M.D., and STEVEN M. HORVATH, M.S., PH.D., Philadelphia, Pennsylvania . . . . . | 543 |
| The Metabolism of Thiocyanate After Prolonged Administration in Man. By F. CORBIN MOISTER, M.D., and EDWARD D. FREIS, M.D., Boston, Massachusetts . . . . .  | 549 |
| Diazomethane Poisoning: Report of a Fatal Case With Autopsy. By EDWARD B. LEWINN, M.D., Philadelphia, Pennsylvania . . . . .   | 556 |
| The Diagnostic Significance of "Burr" Red Blood Cells. By STEVEN O. SCHWARTZ, M.D., and SALVATORE A. MOTTO, M.D., Chicago, Illinois . . . . .  | 563 |

## No. 6—DECEMBER

|   |     |
|---|-----|
| The Occurrence of Atheromatous Lesions After Cauterization of the Aorta Followed by Cholesterol Administration. By J. G. SCHLICHTER, M.D., L. N. KATZ, M.D., and J. MEYER, B.A., Chicago, Illinois . . . . .  | 603 |
| The Vascularization of the Aorta. By J. SCHLICHTER, M.D., and R. HARRIS, M.D., Chicago, Illinois . . . . .  | 610 |
| Premenstrual Intoxication. By EDWARD J. STIEGLITZ, M.D., and SERUCH T. KIMBLE, M.D., Bethesda, Maryland . . . . .   | 616 |
| Parathyrotoxicosis: The Syndrome of Acute Hyperparathyroidism. By S. O. WAIFE, M.D., Philadelphia, Pennsylvania . . . . .   | 624 |
| Lower Nephron Nephrosis: Carbon Tetrachloride Poisoning with a Report of 3 Cases. By CHARLES J. MCGEE, M.D., Richland, Washington . . . . .   | 636 |
| A Clinical Study of an Institutional Outbreak of Acute Infectious Lymphocytosis. By GEORGE R. BARNES, JR., M.D., HERMAN YANNET, M.D., and ROSE LIEBERMAN, Southbury, Connecticut . . . . .  | 646 |
| Clinical Experiences in Parkinsonism with a New Type of Antispasmodic, 3-(1-Piperidyl)-1-Phenyl-1-Cyclohexyl-1-Propanol Hydrochloride ("Artane"). By MICHAEL CANELIS, M.D., FREDERICK J. FARNELL, M.D., and THOMAS HODGE MCGAVACK, M.D., New York, New York . . . . .                                 | 655 |
| The Association of Hypoproteinemia with Severe Tropical Sprue. By GUILLERMO GARCIA LOPEZ, M.D., FERNANDO MILANES, M.D., TOM D. SPIES, M.D., REUBEN LOPEZ TOCA, M.D., THOMAS ARAMBURU, M.D., and HADY LOPEZ, PH.G., Birmingham, Alabama, and Havana, Cuba . . . . .                                    | 660 |
| Effects of Vasodilator Drugs and Other Procedures on Digital Cutaneous Blood Flow, Cardiac Output, Blood Pressure, Pulse Rate, Body Temperature, and Metabolic Rate. By ORVILLE HORWITZ, M.D., HUGH MONTGOMERY, M.D., EDWIN DOWNS LONGAKER, M.D., and ANN SAYEN, Philadelphia, Pennsylvania . . . . . | 669 |

## NEW BOOKS AND NEW EDITIONS

|                                    |      |      |      |      |     |     |
|------------------------------------|------|------|------|------|-----|-----|
| Book Reviews and Notices . . . . . | 119, | 235, | 360, | 482, | 598 | 718 |
|------------------------------------|------|------|------|------|-----|-----|

## PROGRESS OF MEDICAL SCIENCE

## MEDICINE

|   |    |
|---|----|
| Hypotension. By SAM A. THREEFOOT, M. D. . . . . | 86 |
|---|----|

## NEUROLOGY AND PSYCHIATRY

|   |     |
|---|-----|
| Narcolepsy: Brief Review and Report of Cases. By FRANK R. DRAKE, M.D. . . . . | 101 |
|---|-----|

## SURGERY

|   |     |
|---|-----|
| Pericardial and Cardiac Surgery. By HOMER M. SMATHERS, M.D. . . . . | 213 |
|---|-----|

## OPHTHALMOLOGY

|   |     |
|---|-----|
| The Ocular Fundi in Relation to Operations for Hypertensive Cardiovascular Disease.<br>By ROBERT W. HOLLENHORST, M.D., and H. P. WAGNER, M.D. . . . . | 225 |
|---|-----|

## PATHOLOGY AND BACTERIOLOGY

|   |     |
|---|-----|
| The Collagen Diseases. By ERNEST AEGERTER, M.D., and JOAN HUMPHREY LONG, M.D. . . . . | 324 |
|---|-----|

## PREVENTIVE MEDICINE AND EPIDEMIOLOGY

|   |     |
|---|-----|
| Ten Years in the Epidemiology of Mumps. By JOHN E. GORDON, M.D., and LAWRENCE<br>KILHAM, M.D. . . . . | 338 |
|---|-----|

## DERMATOLOGY AND SYPHILOLOGY

|  |     |
|--|-----|
| Drug Eruptions: A Survey of Recent Literature. By HERMAN BEERMAN, M.D. . . . . | 446 |
|--|-----|

## OTO-RHINO-LARYNGOLOGY

|   |     |
|---|-----|
| The Medicated External Auditory Canal. By NOAH D. FABRICANT, M.D. . . . . | 477 |
|---|-----|

## THERAPEUTICS

|   |     |
|---|-----|
| Recent Advances in Parenteral Fluid Therapy. By OSCAR BODANSKY, M.D., Ph.D. . . . . | 567 |
|---|-----|

## RADIOLOGY

|   |     |
|---|-----|
| Electrokymography. By RUSSELL H. MORGAN, M.D. . . . . | 557 |
|---|-----|

GYNECOLOGY AND OBSTETRICS

*Hysterectomy.* By FRANK B. BLOCK, M.D. . . . . 683

PEDIATRICS

Plasma Protein Fractionation in Pediatrics: A Review of its Present Status. By ALFRED  
M. BONGIOVANNI, M.D., and IRVING J. WOLMAN, M.D. . . . . 700

PHYSIOLOGY

*Proceedings of the Physiological Society of Philadelphia* . . . . . 115, 715

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JULY, 1949

## ORIGINAL ARTICLES

### STUDIES OF THE EFFECTS OF FLAVONOIDS ON ROENTGEN IRRADIATION DISEASE

#### 1. PROTECTIVE INFLUENCE OF RUTIN IN IRRADIATED DOGS\*

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School of Medicine and Dentistry)

Prior to the development of the atomic bomb, the effects of intensive ionizing irradiation on mammals were studied only occasionally.<sup>16,26,36,37</sup> The present report deals with some of the factors contributing to the mortality after roentgen irradiation, with particular emphasis on the significance of hemorrhage and sepsis. Attempts were made to reduce the predictable mortality of irradiated dogs and to check the hemorrhagic manifestations by administering flavonol glucosides.<sup>29</sup>

**Methods. Animals:** Young, healthy male or female hound or mongrel dogs of the beagle strain, approximately 1 year of age and of comparable sizes and weights, were used.

They were maintained for a minimum of 4 weeks in quarantine prior to study. During this period they were rested, deloused, dewormed and vaccinated with anti-distemper vaccine. They were maintained for at least 1 week prior to irradiation in individual experimental kennels. They were given a diet consisting of 40:7 mixture of Friskies Dog Food Meal† and Evr Redy Meal§. All animals that developed anorexia in the post-radiated state were given fresh ground beef|| and whole cow's milk, as well as the commercial foods.

Clinical observations were made daily and weights recorded semiweekly. Immediately after death, all organs were examined and sections were taken from all organs and obviously abnormal tissues. After fixation in Bouin's fluid, routine hemotoxylin and eosin stains of the sections were prepared for histopathological study.

\* This paper is based on work performed under Contract No. W-7401-Eng-49 for the Atomic Energy Project at the University of Rochester. The authors gratefully acknowledge the counsel of Dr. H. Blair, director, and Dr. A. H. Dowdy, former director, Atomic Energy Commission, University of Rochester.

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‡ Friskies Dog Food Meal, Albers Milling Company, Peoria, Ill. It consists of a minimum of 24% mixed proteins, 4.5% fat, 10% ash and a maximum fiber content of 4%.

§ Evr Redy Dried Meat with Bone, Rich Products Corporation, Rockford, Ill. It provides a minimum of 60% beef proteins and 5% fat, a maximum of 15% ash and 4% fiber.

|| The consumption of all medication was facilitated by incorporating the drug in approximately 10-20 grams of fresh ground beef. Control dogs were also given an equal quantity of meat 3 times daily.



*Irradiation Technique.* The technique of single dose total body irradiation was used throughout. The dogs were exposed to the irradiations from a Picker industrial x-ray machine of 250 KVP, at a target skin distance of 37 inches. A 14.22 mm. parabolic aluminum and an 0.53 mm. copper filter were used; the half-value layer was 2.15 mm. of copper. The dosage usually delivered to the dorsum of the skin of dogs was 350 r. This value was determined each time from direct measurement in air with a Victoreen ionization chamber at a trial run. The dogs were enclosed separately in individual small wooden boxes fitted with loose open screen tops which permitted movement during irradiation.

*Hematology.* Accepted methods were used in the examination of the peripheral blood.<sup>28</sup> All blood samplings were done by jugular venipuncture without stasis at a standard time of the morning, both pre- and post-radiation, when the animal was in a fasting state. The following elements were measured: Erythrocytes, hemoglobin, white blood cells, volume of packed cells and sedimentation rate. The relative and absolute proportions of neutrophils, eosinophils, basophils, lymphocytes, monocytes, myelocytes, blast and unusual forms were measured in smears of peripheral blood. Erythroblasts and reticulocytes were counted, and an evaluation of anisocytosis, poikilocytosis and basophilic stippling was also noted. The platelets were counted after treatment with a brilliant cresyl blue diluting fluid.

*Experimental. Biologic response to irradiation.* The reactions of animals to whole body irradiation have been described previously,<sup>2,8,13,16,26,27</sup> critical and determining factors being species and dose. In the present study the dogs given a penetrating single dose of 350 r at the target skin distance exhibited no gross external changes for several days, although a leukopenia was detectable within 1-to-2 days. An increase in body temperature was not always detected at this time. Both a thrombocytopenia and an anemia appeared after 4 days, at which time the food consumption of the dogs also began to decrease. Further signs of gastro-intestinal irritability, infrequent vomiting and some diarrhea appeared

somewhat later. Anorexia became profound from the 7th to the 21st day when oropharyngeal ulceration and gingivitis also very frequently appeared. The body weight remained stable during the first week; weight loss was observed in the 2nd and 3rd weeks, after which normal growth was resumed. Hemorrhagic tendencies, observable most frequently as oozing in the gingival margins or petechiae in the unpigmented epidermis of the dog, made their first external appearance about the 10th day. The early appearance of bloody stools, epistaxis or hematemesis in an otherwise healthy appearing dog proved to be of serious prognostic significance, as were a marked lassitude, an unkempt appearance and anorexia to fluids as well as to diet. Twenty two of 37 control dogs (60%) died within 13 to 30 days (average 20 days) after irradiation.

A gross examination of the animals which succumbed always revealed a hypoplasia of the marrow, spleen and lymph nodes associated in general with a panhematopenia. Most frequently associated conditions were petechiae, ulcerations and bleeding into the various portions of the intestinal tract, pulmonary hemorrhages and occasionally indications of a generalized sepsis. Histopathological examination did not indicate overwhelming infection of critical organs such as the lungs, hemopoietic centers and abdominal viscera, and there was no evidence of peritonitis or pleuritis.

*Effect of lemon peel infusion in irradiated dogs.* An aqueous concentrated extract of lemon peel<sup>29</sup> similar to Szent-Gyorgyi's original preparation<sup>30,33</sup> in the form of enteric-coated 200 mg. tablets was given to 11 dogs orally 3 times daily beginning 1 week prior to irradiation and continued until 28 days post-radiation. Four of these

<sup>28</sup> Mr. A. J. Lorenz, Director of the laboratories, and Mr. W. E. Baier, Manager, California Fruit Growers' Exchange, Ontario, California, supplied the lemon peel preparation.

dogs died with typical signs of irradiation toxicity. Only transitory symptoms of intoxication appeared in 2 of the surviving dogs. A routine hematological examination of the entire group of 11 did not indicate any significant difference between it and the control group of 37 dogs not receiving any dietary supplement. Nevertheless, the lemon extract proved effective in increasing the survival of irradiated dogs: 36% (4 of 11) of the supplemented dogs succumbed at an average of 21 days (range, 11 to 31 days) after irradiation compared to the 60% (22 of 37) mortality observed in 20 days in the control dogs.

*Effect of ascorbic acid in irradiated dogs.* The value of citrus concentrates in alleviating experimental and clinical purpura has been ascribed<sup>22,38</sup> to the vitamin C present. Unlike man, the dog ordinarily synthesizes adequate quantities of this vitamin. Furthermore, the vitamin C analysis of the lemon peel preparation was only 1.8 mg. per 200 mg. tablet. It would thus appear that this quantity, insignificant in relation to the dog's dietary consumption, would play no role in the protective effect of the lemon concentrate against irradiation. This was demonstrated in an experiment in which 12 dogs were given 100 mg. of l-ascorbic acid orally 3 times daily beginning 1 week prior to irradiation. Six dogs (50%) succumbed after 12 to 14 days post-radiation, and at autopsy exhibited a typical widespread hemorrhagic diathesis. The clinical course and hematological data of all animals were identical to the control irradiated dogs.

*Effect of rutin in dogs irradiated with 350 r—rutin given both before and after irradiation.* Certain flavonol glucosides have been reported to be

effective in suppressing purpuras of unknown etiology in the guinea pig and man,<sup>14,31</sup> and the active principle has been designated by Szent-Gyorgyi, "vitamin P." Extracts of lemon peel are rich in "vitamin P" activity. Accordingly rutin,<sup>#</sup> a rhamnoside typical of this type of compound, was tested for its effectiveness against the irradiation syndrome in dogs. Marked differences in mortality and morbidity were dependent upon the chronological relationship of onset of rutin treatment to irradiation. First recorded are the observations when rutin administration *preceded* the irradiation and was continued thereafter.

1. *Mortality and incidence of hemorrhage.* Rutin was given orally in 50 mg. gelatin capsules to a group of 27 dogs 3 times daily beginning 1 week prior to irradiation and continued until 28 days post-radiation. The data were obtained in 5 separate trials performed at different times during the year. Control studies were carried out simultaneously. In each trial the results were identical and a summary of the mortality, survival times and clinical evidence of hemorrhage compared to similar data from the control dogs is given in Table 1. The weight curves of the rutin-treated animals, in general, paralleled the weight curves of the control group of animals.

2. *Petechiae formation.* By applying a circular suction cup of 1.8 cm. in diameter at a standard negative pressure of approximately 60 mm. Hg. to the clear unpigmented epithelium of the dog's abdomen for 2 minutes, an attempt was made to study induced petechial formation. This type of procedure provided a crude evaluation of post-radiation hemorrhagic tendencies. In brief, it can be stated that the rutin-treated dogs exhibited fewer and small-

<sup>#</sup> Obtained in generous quantities from the Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia, Pennsylvania, through the courtesy of Dr. J. F. Couch and also the Abbott Laboratories, North Chicago, Illinois.

er induced petechiae than the untreated dogs.

3. *Coagulation time.* Neither the prothrombin nor fibrinogen appeared to be depleted in irradiated dogs, although there was a minor prolongation of the whole blood clotting time.<sup>2</sup> The

drawn venous blood from dogs was placed into tubes and the coagulation time determined.<sup>20</sup> The clotting time before irradiation varied in individuals from 6 to 12 minutes (mean 9) and in the terminal state from 6 to 50 minutes (mean 18). There was a crude

TABLE 1.—THE INFLUENCE OF RUTIN ON IRRADIATED DOGS (350 r)

|               | Number of Dogs |          | Mortality<br>per cent | Survival (a)<br>Post-Radiation<br>average days |            | Exhibiting<br>Gross Bleeding (b)<br>per cent | Showing Petechiae<br>per cent |
|---------------|----------------|----------|-----------------------|--|------------|--|-------------------------------|
|               | at start       | survived |                       |  | range days |  |                               |
| Control       | 37             | 15       | 60                    | 20   | 13-30      | 64   | 84                            |
| Rutin-Treated |                |          |                       |  |            |  |                               |
| Group 1(c)    | 27             | 24       | 11                    | 21   | 16-31      | 22   | 22                            |
| Group 2(d)    | 6              | 4        | 33                    | 16   | 14-18      | 66   | 50                            |
| Group 3(e)    | 5              | 1        | 80                    | 16   | 13-20      | 40   | 100                           |
| Group 4(f)    | 5              | 2        | 60                    | 18   | 11-28      | 40   | 80                            |

a. Calculated from the animals which succumbed.

b. Bleeding from the gingival surfaces, or any of the orifices, nasal, oral or vaginal or hematoma formation.

c. Group 1. 50 mg. rutin, 3 times daily, was given for 7 days before as well as after irradiation.

d. Group 2. 50 mg. rutin, 3 times daily, was given for *only* 7 days before irradiation.

e. Group 3. 150 mg. rutin, 3 times daily, was given *beginning the second day after* irradiation.

f. Group 4. 400 mg. rutin, 3 times daily, was given *beginning the day after* irradiation.

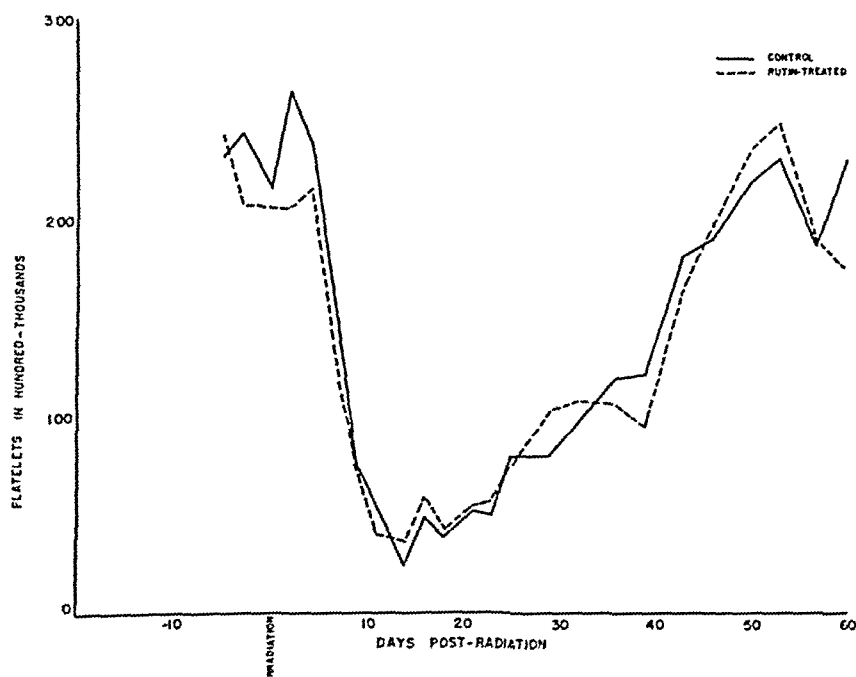


Fig. 1.—Mean platelet values.

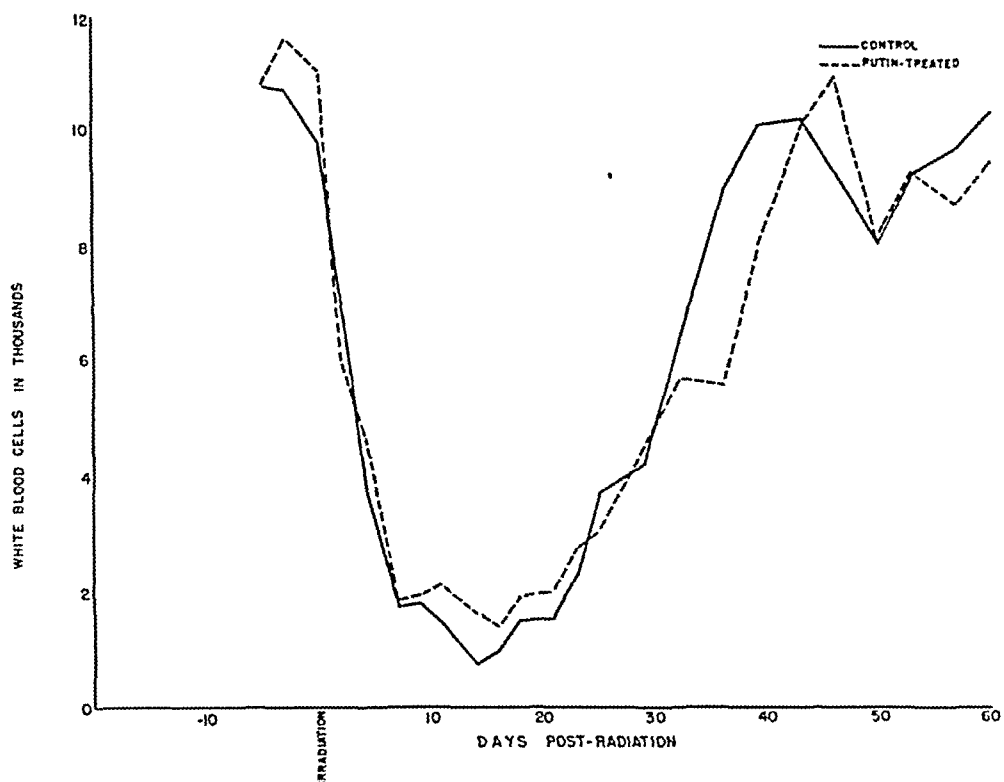


Fig. 2.—Mean white blood cell values.

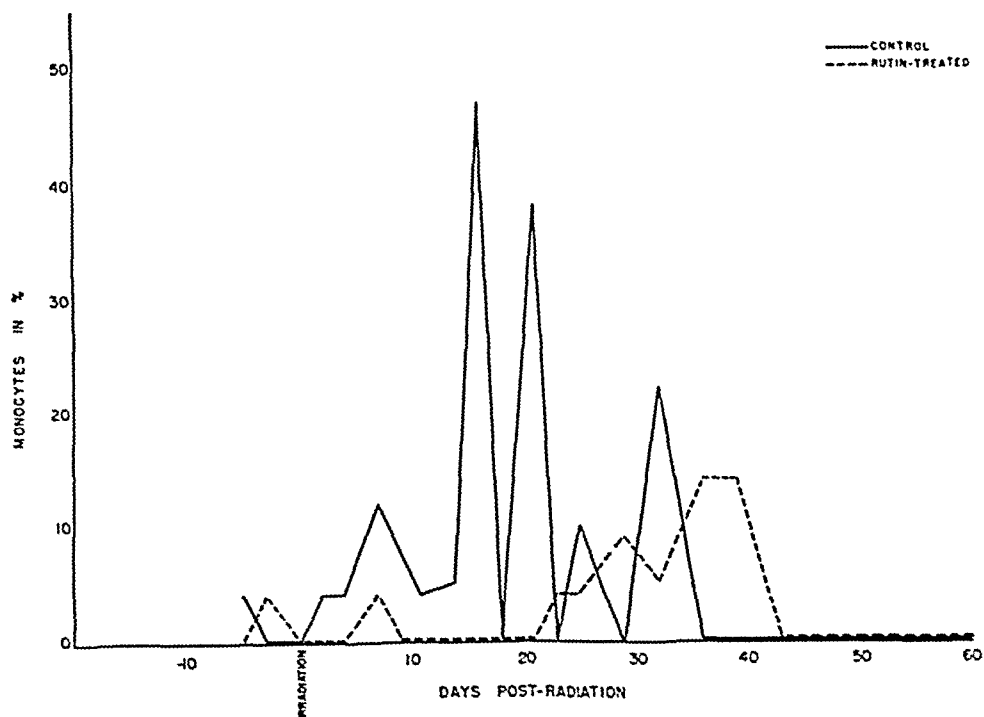


Fig. 3.—Mean monocyte values.

relationship of coagulation time to the hemorrhagic tendency, but at least one animal succumbed to a "hemorrhagic death" with the coagulation time identical with that obtained pre-radiation.

The coagulation time of dogs receiving rutin was similar to that of control dogs.

4. *Hematological changes.* The characteristic changes in the peripheral

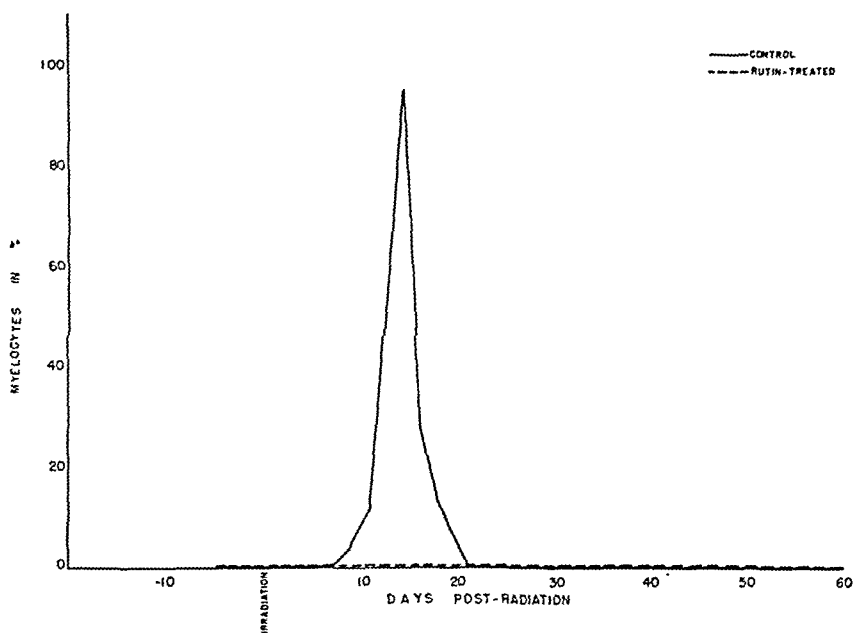


FIG. 4.—Mean myelocyte values.



Fig. 5.—Mean red blood cell values.

blood of dogs exposed to 350 r are given in Figures 1-10, and the findings from dogs treated with rutin are given in the same figures. Each curve represents the means obtained either from the total or surviving dogs in each group.

To summarize the hematological results: a. The thrombocytopenia (Fig. 1) and leukopenia (Fig. 2) of both control and rutin-treated dogs were identical.

b. Similarly, the comparative curves of the total neutrophil and lymphocyte elements exhibited no significant differences. Also there were no significant differences in the quantity of eosinophils or basophils.

c. The comparative estimation of monocytic and myelocytic elements is given in Figs. 3 and 4. The myelocytes of the control dogs were increased from the normal of zero to almost 1% between the 8th and 20th days post-radiation. Also, the leukoblast forms and monocytic cells of the control dogs were significantly increased about this time.

d. The erythrocyte count and corresponding hemoglobin of the rutin-treated dogs declined significantly less rapidly than the control irradiated dogs until approximately the 33rd day post-radiation (Fig. 5). After this day the tendency towards restoration of normal levels was somewhat greater in the untreated dogs.

e. The erythroblasts in the blood of the rutin-treated dogs (Fig. 6) were significantly more numerous than those in the blood of the control dogs from about the 21st to the 43rd post-radiation days. A corresponding increase in the nucleated red blood cells also was seen in the rutin-treated animals from about the 21st to the 47th post-radiation days (Fig. 7).

f. An increase in the basophilic stippling of the red blood cells of the untreated dogs was observed between the 21st and 47th days. The reticulocytes of both rutin-treated and control dogs were similar until between the 39th and 60th days when the count in the surviving control dogs was significantly increased (Fig. 8).

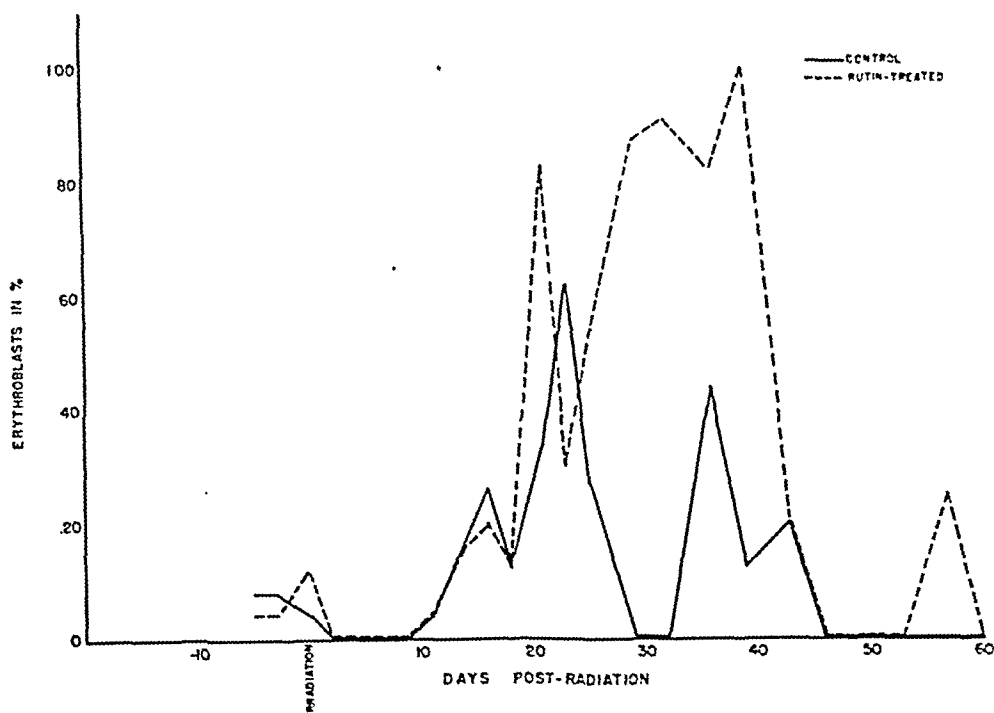


Fig. 6.—Mean erythroblast values.

g. Although there was no great difference in degree of anisocytosis of the red cell elements, it would appear that there was some increase in the degree of poikilocytosis in the control dogs

(Fig. 9) during most of the post-radiation period.

h. The corrected sedimentation rate of the red cells is given in Fig. 10. Although the sedimentation rate of both

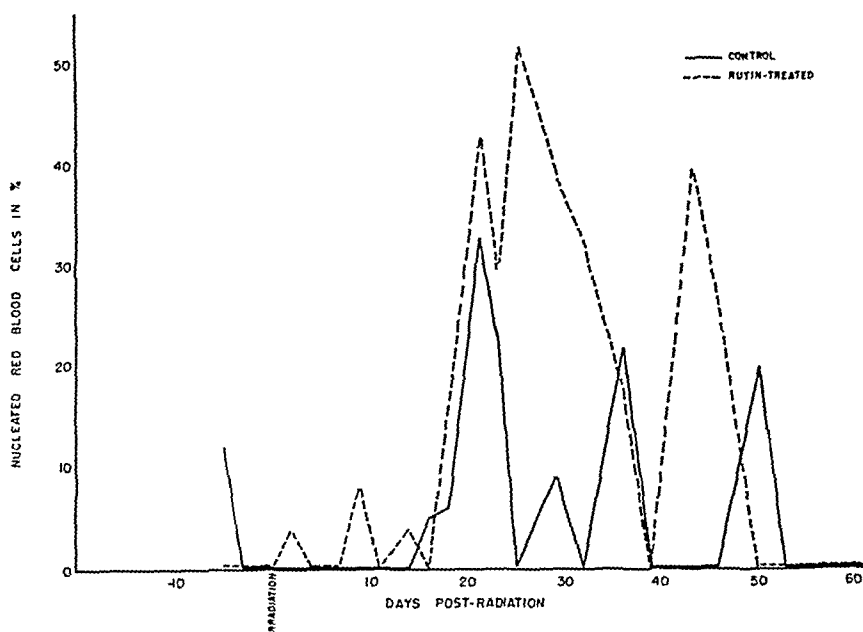


Fig. 7.—Mean nucleated red blood cell values.

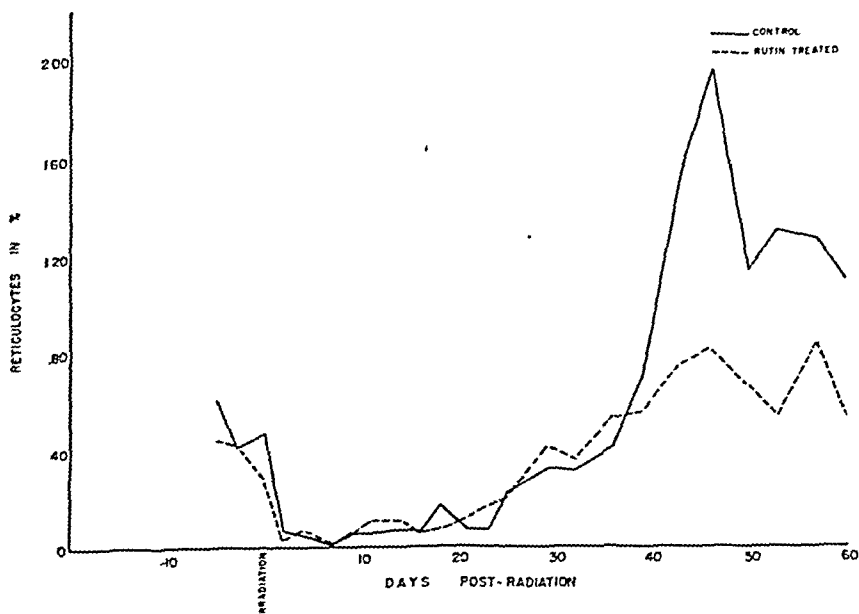


Fig. 8.—Mean reticulocyte values.

rutin-treated and control dogs was shown to increase rapidly in the post-radiated state, the increase of the control dogs was the greater.

5. *Post-mortem examination.* All

animals which succumbed from the effects of irradiation were grossly similar and it was impossible to distinguish the 3 rutin-treated dogs that died from the 22 untreated dogs. Common

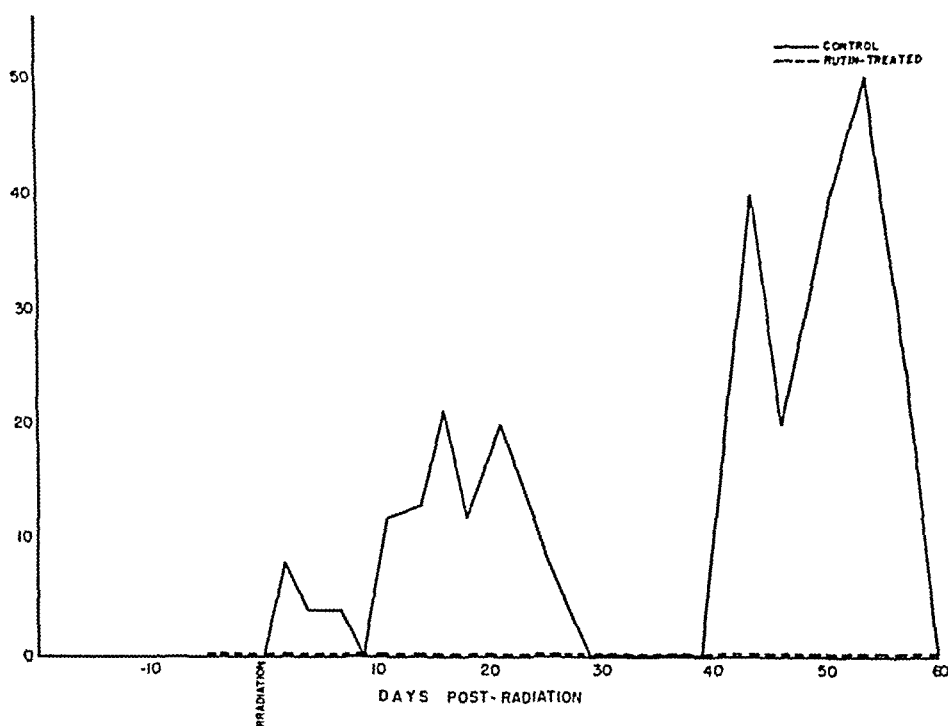


Fig. 9.—Subjective evaluation of poikilocytosis.

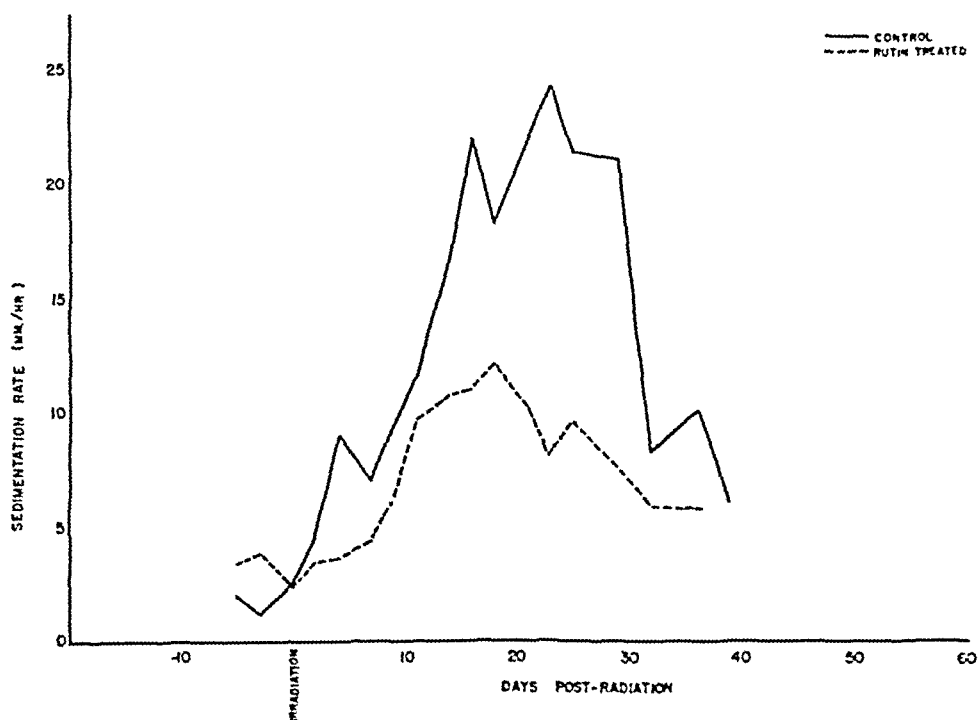


Fig. 10.—Mean sedimentation rates.



findings were hypoplasia of the bone marrow, lymph nodes and spleen, generalized purpura and petechiae formation, intrapulmonary, gastric or intestinal hemorrhage and occasional signs of alveolar and pulmonary sepsis.

Likewise, autopsy examination of all animals in the state of clinical recovery, 35 to 60 days post-radiation, revealed only the anticipated indications of recovery from irradiation toxicity with marrow hyperplasia, hyperemia of the gastric and intestinal mucosa and occasional indication of a previous purpuric state. The spleen and lymph nodes showed considerable variation. The predominating picture was that of hypoplasia or early regeneration.

A careful study of histological sections from the organs of all animals contributed little to the findings of gross organ examination and previous studies<sup>2,8,13,16,20,36,37</sup>. It was impossible to differentiate in any way between the rutin-treated and untreated dogs. Using the usual tissue strains, the morphological state of the vascular systems of both groups appeared identical.

*Effect of rutin in dogs irradiated with 350 r — rutin given pre-radiation only.* Rutin was fed as 50 mg. capsules 3 times daily to 6 dogs beginning 1 week before irradiation. Two of the 6 (33%) died (Table 1). The hemorrhagic tendency and irradiation illness were more severe than seen in the dogs given rutin both before and after irradiation (mortality 11%) but less than that seen in untreated control dogs (mortality 60%).

*Effect of rutin in dogs irradiated with 350 r—rutin given post-radiation only.* In one test rutin was fed as 150 mg. capsules 3 times daily to 5 dogs beginning the second day after irradiation with 350 r. Four of these 5 dogs (80%) died. In a second test 400 mg. were administered 3 times daily to 5 dogs beginning the day after irradiation. Three of these 5 dogs (60%) died. In

the control series 22 of 37 dogs died with a mortality of 60%. A summary of the mortality and hemorrhagic tendencies is given in Table 1. In general, this treatment appeared to have no significant effect on the effect of irradiation disease from examination of the clinical course, the peripheral blood or from post-mortem observations.

*Effect of rutin in dogs irradiated with 450 r — rutin given both before and after irradiation.* The degenerative reaction of dogs to 450 r single dose irradiation was, as to be expected from the data on 350 r irradiation, more acute and lethal. However, in the experience of this laboratory it has been difficult to utilize so large (or larger) an acute dose to attain 100% mortality; that is, an occasional dog survives. Thus, 4 of 5 control dogs given 450 r (80%) died within 14 to 29 days (average 18 days). When 50 mg. of rutin were given orally 3 times daily beginning 1 week prior to irradiation to 4 dogs, 3 (75%) succumbed within 15 to 17 days (average 16 days).

*Studies on the excretion of rutin in urine.* The amount of rutin excreted by dogs receiving 100 mg. daily was determined by the method of Couch.<sup>6</sup> *In vitro* recovery tests on fresh urine and on urine stored for 72 hours indicated an average recovery of the drug of 99%. Only small amounts of rutin were recovered after the 3rd day of administration, and with supplements of 2.8 and 5 gm., usually only small increments in the output were noted (Table 2). Total body irradiation did not appear to affect the urinary excretion of the drug.

*Bacteriological studies.* The flavonols and rutin have some degree of antibiologic activity.<sup>3,24</sup> The development of signs of sepsis in the irradiated dogs and the undisputed contribution of uncombated infection in the absence of adequate leukocytic response to the

TABLE 2.—URINARY EXCRETION OF RUTIN WHEN 100 MG. WAS FED 3 TIMES DAILY

| Dog 1           |                             |                            | Dog 2           |                             |                            |
|-----------------|-----------------------------|----------------------------|-----------------|-----------------------------|----------------------------|
|                 | Days after start of feeding | Rutin in Urine mg/24 hours |                 | Days after start of feeding | Rutin in Urine mg 24 hours |
| Pre-radiation   | 1-2                         | 0.0                        | Pre-radiation   | 1-2                         | 0.0                        |
|                 | 3-5                         | 0.5                        |                 | 3-5                         | 0.8                        |
|                 | 6**                         | 0.3                        |                 | 6-9                         | 2.4                        |
|                 | 7**                         | 2.1                        |                 | 10*                         | 1.8                        |
|                 | 8                           | 8.0                        |                 | 11-14                       | 5.8                        |
| Post-radiation† | 9                           | 2.7                        | Post-radiation† | 15**                        | 3.3                        |
|                 | 11-21                       | 2.0                        |                 | 16**                        | 5.7                        |
|                 | 22**                        | 1.7                        |                 | 17*                         | 2.8                        |
|                 | 23**                        | 7.8                        |                 | 18                          | 7.0                        |
|                 | 24                          | 3.9                        |                 | 19                          | 4.1                        |
|                 | 25                          | 6.2                        |                 | 20                          | 26.6                       |
|                 | 29                          | 0.0                        |                 | 21-25                       | 2.6                        |
|                 | 32                          | 1.8                        |                 | 29                          | 0.0                        |
|                 | 35-50                       | 0.3                        |                 | 31                          | 1.8                        |
|                 |                             |                            |                 | 35-39                       | 0.0                        |
|                 |                             |                            |                 | 42                          | 5.3                        |
|                 |                             |                            |                 | 45-50                       | 0.1                        |

\* Supplementary feeding of 5 gm. rutin.

\*\* Supplementary feeding of 1.4 gm. rutin.

† 350 r single dose total body irradiation.

irradiation syndrome made a bacteriological survey imperative.

Under aseptic conditions, routine blood samples were withdrawn from all irradiated dogs at frequent intervals and in the terminal state. Post-mortem samples were taken aseptically from the heart. The blood was cultured in a variety of nutrient media under both aerobic and anerobic conditions.

No detectable differences were observed in the frequency or type of septicemia between the flavonol-treated dogs and the untreated dogs. For this reason, the data from all blood cultures to date were pooled (Table 3). The organisms isolated and their frequency were: *Clostridium welchii* (16 times), hemolytic streptococcus (7), anerobic gram-positive rod forms (5), *B. coli* (4), *Staph. albus* (3.) and unidentified gram-negative rod forms (3); obtained twice each were *B. subtilis* and *Clostridium fallax*; and obtained once each were *Staph. aureus*, *B. pyocyaneus*, an unidentified staphylococcus, an unidentified diphtheroid form, an unidentified hemophilus organism and a gram-positive aerobic rod.

TABLE 3.—A SURVEY OF BLOOD CULTURES TAKEN FROM IRRADIATED DOGS

|                     | Positive | Total | % Positive |
|---------------------|----------|-------|------------|
| Pre-radiation       | 0        | 25    | 0          |
| Post-radiation      | 7        | 114   | 6.1        |
| 0-7 days            | 5        | 70    | 7.1*       |
| 8-30 days           | 25       | 280   | 8.9        |
|                     | 7        | 86    | 8.1*       |
| 48 hours pre-mortem | 13       | 28    | 46.4       |
| 24 hours pre-mortem | 13       | 21    | 61.9**     |

\* Data from dogs eventually succumbing to irradiation toxicity abstracted from the total number.

\*\* These data confirm the observations of Warren and Whipple<sup>37</sup> which demonstrated that direct x-irradiation to the abdomen produces destruction of the intestinal epithelium, but a bacterial invasion of tissues, lymph or blood by bacteria does not occur until the agonal state. This situation, as they point out, is quite common to other conditions.

*Effect of whole body irradiation on the fragility of the red blood cells.* The rate at which anemia developed in the dogs continuously treated with rutin was significantly less than in the control dogs following whole body exposure to 350 r irradiation (Fig. 5). A suggestion was entertained that the red cell membrane is weakened in

irradiated dogs, producing some disintegration *in vivo*.<sup>19</sup> This was investigated by examining the resistance of erythrocytes from irradiated dogs to induced hemolysis. In the procedure adopted duplicate determinations were made with saline solutions differing from tube to tube by 0.02%, and the end point of hemolysis was determined with a photoelectric colorimeter.<sup>17</sup> Serial determinations of blood samples withdrawn from a variety of normal non-radiated and irradiated dogs, many in the terminal state with profound purpuric manifestations, consistently provided cell lysis beginning at 0.40 and completed at about 0.80% saline solution with no differences between irradiated and non-radiated dogs.

**Discussion.** An appreciation of the action of flavonols in the irradiated dog provokes an acknowledgment of the uncertainty surrounding the irradiation disease. As yet, there is no agreement as to the individual significance of sepsis, hemorrhage or the nondescript toxic action of irradiation products in the terminal course.<sup>26,27,29,36,37</sup> In certain irradiated animals there is little question of the terminal role of hemorrhage into vital organs.<sup>2,7,8,21,26,27,34,35</sup> In others where this was less obvious, it has been convenient to attribute the exitus to the effects of sepsis.<sup>34</sup> Finally, there are those animals who succumb before either hemorrhage or sepsis could be expected and these do not exhibit any obvious understandable cause of death.

The significant reduction in the hemorrhagic diathesis seen in the 350 r irradiated dogs treated pre- and post-radiation with rutin suggests that through reducing the hemorrhagic tendency the glucoside exerts its sparing action on the predictable rate of mortality. The failure of rutin to spare dogs treated *after* irradiation requires some consideration. Data from this report suggest that the dog is relatively un-

saturated in regard to the flavonol as measured by a lapse of several days before rutin can be detected in the urine. Apparently, during the pre-radiation period the dog is able to saturate itself, and presumably this provides for maintenance or repair of an altered vascular system. This would explain the partial effectiveness of giving rutin even in relatively small doses of 50 mg. 3 times daily for 1 week up to the time of irradiation, but not after. In the face of decreased alimentary absorption following irradiation<sup>4,23</sup> it is probable that the rutin available after oral administration would be limited, and thus it cannot exert its maximum therapeutic effect. The failure of rutin to alter the increased lethal effects of 450 r irradiation in dogs is at the moment a matter of conjecture. It appears, however, that rutin controls the hemorrhagic tendency which is a predominant factor in mortality in mid-lethal irradiation (350 r). At higher doses hemorrhage appears to be less responsible than a generalized intoxication for death. It is this non-specific reaction which is the primary cause of mortality in acutely irradiated rats, mice and guinea pigs in which rutin offers little or no protection.<sup>12</sup>

Since the flavonol glucosides have been shown to have antibiotic activity,<sup>3,24</sup> it is necessary to consider the role the drug would play in combating the sepsis which follows irradiation. Terminal septicemia following irradiation was exhibited in no more than 62% of dogs so studied, and it appears unlikely that rutin antibiosis would significantly benefit the survival rate.

Allen and Jacobson<sup>1,2</sup> have recently reported that the level of heparin or a heparin-like agent in the blood of irradiated dogs was increased, and to this was attributed the hemorrhagic manifestations. The injection of such antiheparin agents as toluidine blue and protamine temporarily restored the

prolonged coagulation time to normal and halted the purpuric manifestations. Rutin, *per se*, did not reduce the hypo-coagulability of blood from irradiated dogs. In a subsequent report the relationship of rutin and heparin will be discussed but there is no evidence to indicate that rutin can restore the prolonged coagulation time produced with heparin. Uniformly, however, all dogs had a reduction of the peripheral platelet count which was correlated with obvious depression of marrow activity. It has been observed that heparin, *per se*, can induce a thrombocytopenia,<sup>10</sup> and this presumably results secondarily to a visceral clumping of platelets.<sup>5</sup> However, the intimate time relationship of thrombocytopenia with onset of hemorrhagic syndrome has impelled the natural conclusion that the two were inseparable.<sup>8,32</sup> In the present observations in irradiated dogs, severe prolonged thrombocytopenia could be dissociated from the purpuric manifestation by the administration of rutin.

An interpretation of the hematological differences uncovered between irradiated dogs with and without pre- and post-radiation rutin therapy invites considerable speculation. In summary, there was found (a) a more rapid decline of the erythrocyte count in the untreated dogs, (b) a significant elevation in erythroblasts and nucleated red blood cells between the 20th and 45th post-radiation days in the rutin-treated dogs, and (c) an increased reticulocyte response between the 30th and 60th post-radiation days and an increased basophilia of the erythrocytes between the 20th and 50th post-radiation days in the untreated dogs.

Assuming that vascular dysfunction permits increased diapedesis to occur during the early post-radiation period before arrest of erythrocyte maturation in the bone marrow would significantly reduce the peripheral concentration of

red cells, it appears plausible that prevention by rutin of increased diapedesis would serve to maintain the total blood count. This is the more likely explanation in the absence of a positive effect of the flavonol glucoside on the irradiated marrow or positive indication that erythrocyte fragility is increased in the irradiated dog.

An increased reticulocyte response usually characterizes augmented erythropoiesis. The greater reticulocyte response of the 15 surviving untreated dogs was matched against the average reticulocyte count of 24 surviving rutin-treated dogs. The dogs receiving rutin did not suffer the low ebb of anemia to which the untreated dogs fell, and therefore the recovery stimulus to the untreated dogs was conceivably the greater. This idea was supported by directly comparing the reticulocyte counts of several rutin-treated dogs who had as severe an induced post-radiation anemia as the untreated dogs. Here the recovery curves of both erythrocytes and reticulocytes were very similar.

We have not observed rutin to alter an induced change in capillary permeability in animals. In the absence of a more realistic explanation for this and an invariable increased spontaneous petechiae formation and other signs of purpura following irradiation, it is proposed that the irradiation syndrome stems from a localized reduction in the structural strength or a dysfunction of the vascular system, permitting disruption and uncontrollable diapedesis. It would appear that the prevention of otherwise fatal exsanguination or embarrassment by hemorrhage of vital organs through this route might provide a life-saving support until the ordinary synthetic capacity of the organism can recover from the inhibitory effects of roentgen irradiation. In this regard, it is pertinent to mention that at least 6 dogs given the

flavonol therapy have been observed to survive with minimum hemorrhagic signs in the presence of prolonged (10 to 18 days) drastic leukopenia and thrombocytopenia. In distinct contrast, recovery of untreated dogs with persistent, severe depression of the same blood elements has rarely been observed in this laboratory. To what extent "vitamin P" substances protect against the anaphylactic and histamine factors reported to occur following ionizing irradiation<sup>2,9,23</sup> remains to be clarified.<sup>12</sup>

It is imperative to offer some clarification in the confusion presented by the use of the terms capillary "permeability" and "fragility" in the accumulating literature on "vitamin P". In no test reported here have we given data which would substantially support a claim that rutin *per se* affects the specific membrane permeability phenomenon. In experiments still in progress such confirmative and specific observations have yet to be made. However, it is felt that in some manner, as yet not elucidated, the rhamnose glucoside aids in the control of vascular dysfunction of dogs given 350 r whole body x-irradiation when the substance is given both pre- and post-radiation. Prevention of vascular damage reduces the hemorrhagic extravasation. The extent to which this is limited to the capillaries is a topic for further investigation.

The failure of vitamin C to affect the course of irradiation toxicity, which has also been reported elsewhere,<sup>1</sup> is in contrast to the significant protection given by rutin. With these findings, support is given to the long contested claim by Szent-Gyorgyi and his collaborators<sup>30,33</sup> that a factor, such as "vitamin P", does exist. It is unfortunate that recent efforts in this field deal only with isolated pharmacological characteristics and indirect types of biological assay of the family of flavonoids to which some "vitamin

P" activity is attributed.<sup>15,25</sup> In the main, other investigations have utilized the epinephrin-sparing action of the "active" agents. The work presented here presumably involves an alteration in vascular function with "vitamin P" substances reducing the rate and manner of this dysfunction. Thus, the roentgen irradiation type of dog assay presents itself as an objective method of direct biological test for "vitamin P" potency. With this method it has already been possible to demonstrate that, with reference to rutin, considerable variation exists in closely related compounds.<sup>11</sup>

**Summary.** 1. In dogs given 350 r single dose total body x-irradiation, 60% (22 of 37) untreated animals died, whereas when a preparation from lemon peel was administered continuously pre- and post-radiation, 36% (4 of 11) of the animals succumbed. When the flavonol glucoside, rutin, was administered continuously pre- and post-radiation, 11% (3 of 27) of the animals succumbed; when given pre-radiation only, 33% (2 of 6) dogs succumbed; when given post-radiation only, 80% (4 of 5) and 60% (3 of 5) dogs succumbed.

2. Clinical signs and post-mortem evidence of a hemorrhagic diathesis were most prominent in the untreated dogs and the dogs given rutin post-radiation only. A generalized purpura was observed in the dogs tested with lemon peel extract or rutin, but petechiae and spontaneous purpura were less frequent in dogs given rutin before and after the irradiation than in dogs not receiving rutin. The reduction in hemorrhagic signs existed despite a depression of the blood platelets. Moderate hypocoagulability existed in both control and rutin-treated dogs.

3. Hematological studies indicated that the rate of anemia production and the magnitude of the increased sedimentation rate were reduced while the

erythroblast forms and nucleated red blood cells were increased in the routinely treated animals. Irradiation of dogs with 350 r did not increase the fragility of erythrocytes.

4. Septicemia was demonstrable in no more than 62% of the dogs terminally. Thus, it is suggested that a primary cause of death in the 350 r single dose total body x-irradiated dogs is a

bleeding tendency which may be associated with a vascular dysfunction as well as a thrombocytopenia.

5. The existence of an entity such as "vitamin P" affecting vascular fragility is supported by the present report. The technique of roentgen irradiation to induce a bleeding tendency in dogs may prove useful in an assay for "vitamin P" potency.

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# EVIDENCE ON THE GENESIS OF CERTAIN COMMON NASAL DISORDERS\*

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PROETZ<sup>28</sup> and Polson<sup>26</sup> among others have presented evidence which indicates that swelling of the turbinates, obstruction and hypersecretion in the nose, from whatever cause, may predispose the individual to "common cold", as well as to more chronic, recurrent disorders of the nasal and paranasal spaces including sinusitis.

Dochez and his associates<sup>5</sup> have adduced strong evidence to indicate that this process of nasal hyperfunction is often initiated by a filterable virus with the ultimate production of a typical "common cold". On the other hand, the work of other observers<sup>1,2,15</sup> has indicated that viruses are not responsible for all such reactions of nasal hyperfunction. Other stimuli and situations which have been observed to provoke vascular engorgement, swelling, hypersecretion and obstruction in the nose are: inhalation of irritant dusts and chemical fumes<sup>16,24</sup>, bright lights<sup>23</sup>, chilling of the body surface<sup>10,22,29</sup>, inhalation of pollens and the other substances to which the subject is "sensitive"<sup>11,34</sup>, menstruation and preg-

nancy<sup>20,21</sup>, sexual excitement<sup>17,25,32</sup>, and life experiences which engender insecurity and conflict<sup>4,27,33</sup>.

In an attempt to illuminate further the role of nasal hyperfunction in the natural history of chronic nasal disorders, man and his nose were investigated as a unit. Cognizance was taken not only of changes observed in nasal function, but also of the life setting in which these alterations in nasal function occurred, attention being focused on the emotional reactions, attitudes and behavior of the individual. Some of the observations and conclusions evolving from this method of clinical investigation are detailed in this communication. Some have been presented elsewhere<sup>15,35</sup> and a more detailed and comprehensive report has been assembled as a monograph<sup>12</sup>.

**Method.** Observations were made from 1 to 7 times weekly and for periods lasting from 1 to 8 months on 112 subjects, varying in age from 13 to 60 years. They were examined under uniform conditions at approximately the same time each day.

**Examination of Nasal Structures.** A warmed nasal speculum illuminated by reflected light

\* Supported in part by grants from the Commonwealth Fund and the estate of Lester N. Hofheimer.

from a daylight bulb was used for examination of the nasal structures. The degree of engorgement and swelling of the turbinates, the amount of secretion and the degree of nasal obstruction were estimated in terms of 0 to 4 plus in accordance with well defined standards<sup>13</sup>. Measurements of blood flow were made by comparing the color of the nasal mucous membrane with a suitably calibrated color chart<sup>23</sup>. The colors, quantitated by the method of Munsell, ranged from a pale yellow-red to a deep cardinal, and were expressed as numbers from 0 to 100. It has been shown elsewhere that color changes in mucous membranes reflect variations in blood flow<sup>30</sup>. In addition to these changes, the following were also carefully noted: (1) awareness of accumulated secretion in the nasal cavities; (2) sneezing; (3) burning or tickling sensations; (4) post-nasal drip; (5) pain. The latter was roughly quantitated in terms of 0 to 10 plus, 10 plus representing pain of the highest intensity in the subject's experience.

Elsewhere<sup>13,14,36</sup> it has been demonstrated that the inhalation of noxious chemical fumes or allergens elicits a prompt and appropriate pattern of defense at the head end of the organism, consisting of hyperemia of the nasal mucous membranes, swelling of the turbinates, hypersecretion, and obstruction to breathing. This appeared to represent an attempt to shut out, neutralize, and wash away the noxious agent. A similar pattern of nasal hyperfunction occurred following other threats to bodily integrity which included: (1) experimentally induced pain; (2) cutaneous chilling; (3) exposure to cold atmosphere; and (4) discussion of pertinent emotional conflicts attended by feelings of humiliation, frustration, resentment and guilt engendered by a life situation which had special significance because of the individual's past conditioning experiences. Thus it appeared that the defensive pattern of shutting out, neutralizing and washing away in the nose can be called into play by the organism when its integrity is endangered by a wide variety of direct and symbolic threats and assaults. In some instances, the hyperfunction was well tolerated,

but in others it was associated with nasal symptoms.

The following protocols are representative of more than 4,000 observations on 112 patients carried out in an attempt to determine the relevance of changes in the nose which accompany emotional stress, to tissue damage and nasal disease, and to explore the underlying neural mechanism for the production of such nasal hyperfunction.

#### 1. TISSUE CHANGES IN THE NOSE IN RESPONSE TO SITUATIONAL THREATS ENGENDERING CONFLICT

*Sustained nasal engorgement with pain in association with resentment, frustration and guilt. Observation 1.* A 25 year old physician of Scotch-English extraction, was observed daily 6 days a week for 8 months. He was warm and friendly in his inter-personal relations and aggressive, energetic and self-confident in his approach to his job. His system of security depended predominantly on 3 factors: the approval of his superiors; his ability to be assertively independent in the economic and social spheres; his achievement of a recognized position in competitive society, "success" in his "career".

Shortly after the birth of his first child, his mother-in-law came to visit. The domineering manner in which she dictated the care of the infant and regimented her daughter's convalescence were intensely resented by the subject. He interpreted her behavior as a threat to his position as head of the household and as casting doubt on his judgment as a physician. Soon the situation became intolerable to him. After much misgiving and procrastination, he finally had a "talk" with his mother-in-law, following which she was less aggressive. The subject, though tense, angry and guilty, was gratified to regain his place as head of the family.

During the episode of suppressed resentment there was observed marked sustained nasal hyperfunction (shown graphically in Fig. 1), characterized by hyperemia of the membranes, swelling, hypersecretion and obstruction. These changes were accompanied by restlessness, loss of appetite, flushed face, and a dull, aching "sinus pain" located deep under the bridge of the nose and spreading out over the zygomata (Fig. 2). Following resolution of the difficulty the nasal hyperfunction subsided and pain disappeared.

Comment. Nasal pain was frequently encountered in other subjects during



periods of mucosal hyperemia and swelling occurring in response to life situations engendering conflict, with anxiety and resentment<sup>13</sup>. The subjects were aware, during such periods, of discomfort in both nostrils which at

times developed the quality of a burning pain of 1 to 2 plus intensity, increased by forced inspiration to 4 plus intensity. There occurred, usually with the burning pain, a dull aching pain deep under the bridge of the nose of 1

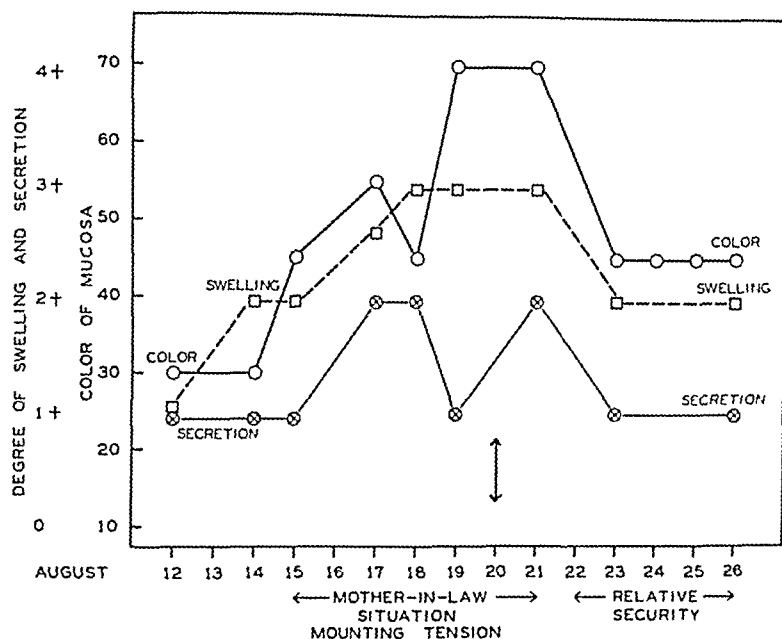


FIG. 1.—Nasal changes during periods of anxiety and conflict regarding the activities of an officious mother-in-law and threat to subject's independence.

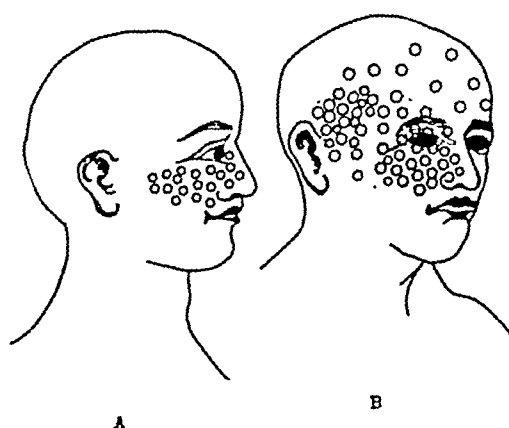


FIG. 2.—Distribution of pain during periods of stress, A, associated with brief periods of swelling and reddening of the turbinates, increased secretion and obstruction predominantly on the right. B, associated with sustained swelling and reddening on the right (during an attack diagnosed as "sinusitis") with photophobia, lacrimation, congestion of the conjunctiva on the right, and flushing of the whole face. There was some intense erythema and "hyperalgesia" over the zygoma.

to 4 plus intensity, which was experienced as well in the orbits, the upper teeth, and along the zygomata. The pain was most often unilateral, occurring on the side of the swollen nasal structures. When the swelling shifted to the opposite nasal cavity, the pain correspondingly changed position. When, in a setting provocative of conflict and anxiety, nasal hyperfunction was marked and prolonged for days or weeks, pain occurred bilaterally over the face in the location described. Pain was intensified by bright lights and a tight collar. It was worse during the working day, increased during periods of stress, and was less intense in the

impulses responsible for "sinus headache". Further, noxious stimulation of these intranasal structures caused spread of pain into the areas of the head, as represented in Fig 2. As previously observed in the skin<sup>31</sup>, stomach<sup>37</sup> and bladder<sup>19</sup>, the swollen, hyperemic mucous membrane of the nose was often found to be accompanied by a lowering of the pain threshold<sup>18</sup>.

*Nasal Exudate and Pus Cells. Observation 2.* The same 25 year old physician described above had presented for evaluation the results of his recent investigations. His senior associate expressed dissatisfaction with the arrangement of the material and was unsympathetic with the formulation. The sub-

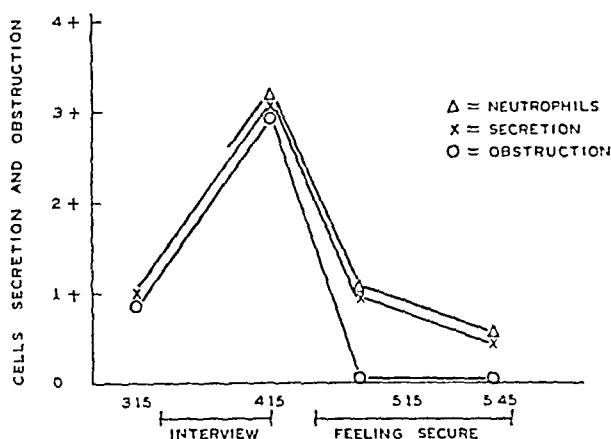


Fig. 3.—Neutrophilic reaction with hypersecretion and obstruction to breathing in the nose accompanying feelings of resentment, frustration and humiliation during interview of a physician with his senior associate.

early morning and late evening. When the pain became relatively intense, superficial and deep hyperalgesia developed in areas of spread of pain, along with photophobia and injection of the sclera on the same side. These symptoms were not dependent for their occurrence on demonstrable pathological involvement of the paranasal spaces.

Evidence has been presented elsewhere<sup>18</sup> demonstrating that the ostia, ducts and turbinates in the nose are far more pain-sensitive than are the linings of the sinuses themselves, and are the site of origin for most of the noxious

ject, reacting to this situation with resentment and feelings of frustration and humiliation, again developed nasal obstruction and hypersecretion. (Fig. 3.) The secretion was thick, viscid and gray-yellow in appearance and contained a large number of neutrophils as compared with previous control observations. The neutrophils diminished in number and the nasal hyperfunction subsided one hour after the interview, as the subject became relaxed and regained relative security.

*Eosinophil Response in the Nasal Secretions. Observation 3.* A 36 year old white male college graduate and beer salesman suffered from chronic vasomotor rhinitis. During an interview which occurred in a setting of an acute reactive depression, frank weeping ensued on several occasions as he discussed his difficulties with interpersonal

adjustments and his failure to achieve success and stability in the economic sphere. His dominant feelings included resentment, frustration, guilt and humiliation. Accompanying the pronounced nasal hyperfunction (Fig. 4), was: (1) a sharp increase in the number of eosinophils and neutrophils in the nasal secretions; and (2) a rise in the number of eosinophils in the blood from 50 per cu. mm. to 220 per cu. mm. (Fig. 4).

Following the weeping episodes, as the subject became relatively tranquil, nasal

striction of the head by a tight steel band<sup>12</sup>.

From these data and those recorded by the two foregoing observations it would appear that neutrophilia and eosinophilia in the nasal secretions occur in response to various threats and assaults as part of the same broad biological protective pattern of defense which includes hyperemia, swelling,

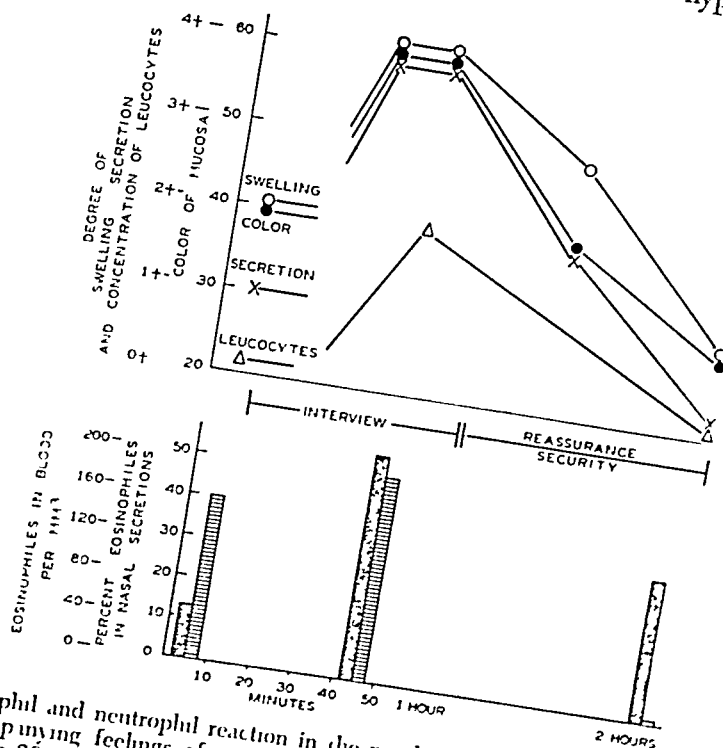


FIG. 4.—Eosinophil and neutrophil reaction in the nasal cavities with nasal hyperfunction and weeping accompanying feelings of resentment, frustration, humiliation, and guilt during an interview with a 36 year old beer salesman (Stippled bars represent blood eosinophil counts)

hyperfunction subsided, the phagocytic white blood cells almost disappeared from the scanty nasal secretions and the number of eosinophils in the blood approached the control level

hypersecretion and obstruction in the nose.

**Comment.** Evacuation of both neutrophilic and eosinophilic leukocytes has also been observed not only after the inhalation of pollen but following direct noxious stimulation of the nose by ammonia fumes and painful con-

**Biopsy Evidence of Edema, Engorgement of the Vascular Lymphatic Channels, and Glandular Hyperfunction in the Nasal Mucous Membrane.** Observation 1 During a period of good spirits and relative freedom from nasal disturbance the same 30 year old white male described in Observation 3 above was subjected to a vigorous discussion of fundamental personal conflicts. At the outset of the interview the nasal structures were of

relatively normal appearance. The color of the mucous membrane was 40, secretion was minimal and both lower turbinates appeared

slightly violaceous. There was 2 plus swelling and obstruction on the right and 3 plus swelling and obstruction on the left. Im-



FIG. 5.—Biopsy from the nasal mucous membrane of a 36 year old male with chronic vasomotor rhinitis before and after interview engendering nasal hyperfunction and conflict (See Obs. 4). A. Biopsy of the left lower turbinate obtained before interview when nasal function was within average limits. Section shows low grade chronic inflammation, relatively undilated vascular and lymphatic channels, and compact, quiescent mucous glands. There is no edema of the stroma. B. Biopsy of the right lower turbinate obtained 1 hour after the biopsy in (A) above, at the point of maximal nasal hyperfunction accompanying verge of tears and feelings of conflict. Section shows prominent, dilated vascular and lymphatic channels, active mucous glands containing masses of stagnated secretion, and edema, as indicated by the lighter value of the stroma. (x 200, Masson's Trichrome Stain.)

mediately after this observation a biopsy\* was made of the left lower turbinate under local 10% cocaine anesthesia. As shown in Fig. 5A, the section revealed essentially normal mucosal structure with a moderate round cell infiltration. During the next hour, as the subject discussed his lack of success in his job, his inadequate sexual adjustment and inability to assume his responsibilities as a husband and father, and his difficulties with his father-in-law, he became restless and agitated and approached the "verge of tears". His feelings were those of resentment, frustration,

be prominent and dilated. The lighter stroma was indicative of edema.

**Comment.** It then became apparent that when the pattern of nasal hyperfunction, which is designed for short term use, is sustained and intense, pathological tissue changes may ensue. Thus the maintenance of persistent nasal hyperfunction proves a costly and inappropriate way to deal with

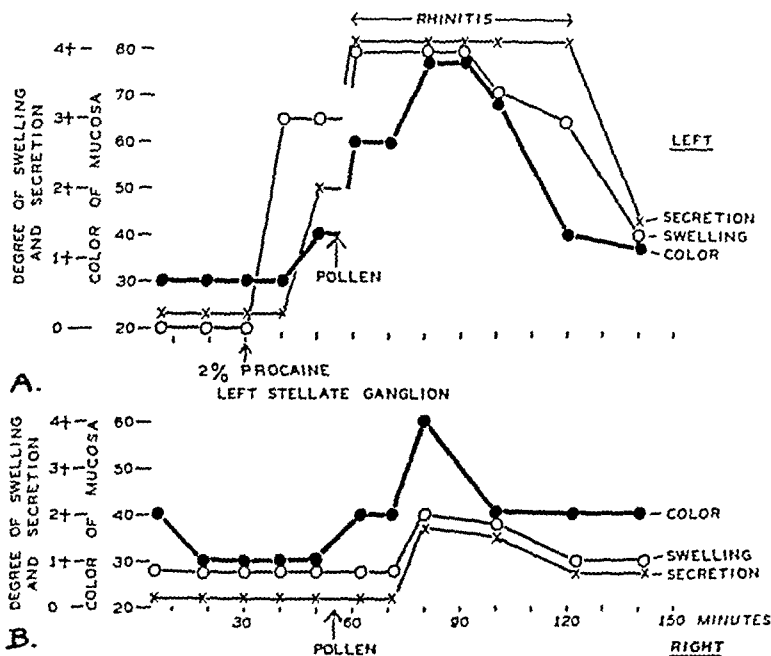


FIG. 6—A. Hyperemia, hypersecretion and swelling in the left nasal cavity following left stellate ganglion blocks with 2% procaine. B. Production of "hay fever rhinitis" following introduction of 2 mg. mixed rag weed pollen on to the acutely and intensely hyperfunctioning mucous membrane in the left nasal cavity. Note that hyperfunction in the right nasal cavity following introduction of pollen was delayed in its appearance and of low intensity.

humiliation and guilt. At this point, 1 hour after the first biopsy, examination revealed the mucous membrane in the right nasal cavity to be deep violaceous red (70)† with 1 plus swelling, secretion and obstruction. A second biopsy was then obtained under local 10% cocaine anesthesia from the right lower turbinate. As shown in Figure 5B it revealed the mucous glands to be filled with secretion and the vascular and lymphatic channels to

adverse life situations.

**2. NEURAL MECHANISMS OF NASAL HYPERFUNCTION IN RESPONSE TO THREATS AND ASSAULTS ON BODILY INTEGRITY.** *Nasal Function Following Brief Unilateral Stellate Ganglion Block. Observation 5.* Following suitable control observations on nasal function (Fig. 6), 6 cc. of 2% procaine was injected into the left stellate ganglion of

\* We are indebted to Dr. Gervais Ward McAuliffe, Associate Professor of Clinical Surgery (Otolaryngology), Cornell University Medical College, for performing the biopsy and to Dr. Nathan Chandler Foot, Professor of Surgical Pathology, Cornell University Medical College, for the preparation and interpretation of the microscopic sections.

† We are indebted to Dr. Bronson S. Ray, Professor of Clinical Surgery, Cornell University Medical College, for performing the surgical procedures.

† Degree of color.

a 58 year old negro male who suffered from seasonal hay fever. Accompanying the other objective signs of the unilateral Horner's syndrome which resulted were hyperemia, swelling, hypersecretion, with moderate obstruction to breathing in the left nasal cavity (Fig. 6).

**Comment.** This observation suggests that impulses mediated by cholinergic fibers in the greater superficial petrosal nerve are responsible for the production of the pattern of nasal hyperfunction described in this report and is in agreement with the work of other investigators<sup>3,7,8,9</sup>.

*Effect of Sustained Noxious Stimulation on the Already Hyperfunctioning Nasal Mucosa.* Observation 6. At the point of maximal nasal hyperfunction 20 minutes after the stellate block described above (Fig. 6A), 2 mg. mixed ragweed pollen were introduced into each nasal chamber. The response of additional hyperemia, swelling, hypersecretion and obstruction on the left side was intense and dramatic and the symptoms produced in the left nasal cavity were those of "hay fever" (Fig. 6B). In the right nasal chamber, however, the hyperfunction was delayed in its appearance and was not of sufficient magnitude to produce symptoms.

**Comment.** This experiment indicates that during the phase of intense nasal hyperfunction induced by stellate ganglion block, the functionally altered mucous membrane reacts promptly and vigorously to contact with a noxious agent, culminating in frank manifestations of nasal disease. On the other hand, the introduction of pollen into the functionally intact mucous membrane in the absence of pre-existing hyperfunction, even in a known "hay fever" sufferer, induced only a transient hyperfunction which was well tolerated.

*Recurrent and Chronic Rhinitis Occurring in a Life Setting Provocative of Conflict, Anxiety, Resentment and Insecurity.* From the study of 100 patients with chronic recurrent nasal disorders, it was possible to establish in many a close correlation between the

occurrence of symptoms and certain life situations giving rise to conflict with anxiety, resentment and frustration. The following case history is a representative example.

*Observation 7.* A 27 year old married housewife with a long standing history of "nose trouble" complained of nasal obstruction, sneezing and profuse watery nasal discharge most severe during the preceding 7 months.

At the age of 3, her parents died of pulmonary tuberculosis and her childhood under the supervision of a series of responsible but unaffectionate relatives was remarkable for the lack of stability and continuity in care. Aged 5, she was adopted by a "highly educated", driving couple who were enthusiastically interested in the betterment of their community and given to lively arguments, not only about the child's care but about other topics of mutual concern. Also living in the household was an older daughter and a kindly, gentle physician. The latter was the only one who freely gave affection to the patient and he soon became a significant symbol of security to her.

Although her general health was good, the patient had, throughout her childhood, frequent "head colds". Her first serious attack of nasal disease occurred at age 20 when her friend and confidant, the elderly physician, died. She reacted to his loss with feelings of intense grief accompanied by weeping. She felt deserted and became fearful of losing others whom she loved. Again, 1 year later, an exacerbation of nasal symptoms occurred in the setting of a family argument which engendered in the patient intense feelings of insecurity and considerable anxiety and resentment concerning the instability of her home and family. Following this attack she underwent a submucous resection.

She married, with her parents' approval, shortly after her graduation from college, and in the security and tranquillity of her own home she remained free from symptoms. Her first pregnancy, 18 months later, was uneventful and during the antepartum period she enjoyed the unqualified "support" of both her husband and her obstetrician.

The last attack of severe nasal symptoms began during the third month of her second pregnancy when another obstetrician told her that she had "heart trouble", that she would have to be "watched closely", and that her circulatory disorder would preclude the use of general anesthetic during delivery. At about the same time her husband enlisted in the Navy. Symptoms continued unabated throughout the pregnancy. Her labor was

long, the delivery difficult and she became intensely resentful of the obstetrician whom she felt had allowed her to suffer unnecessarily. Two days after her return home from the hospital, her husband reported for active duty and she felt lonely, deserted, frustrated and tearful, and her nasal symptoms became incapacitating.

Examination of her nose in March, 1944, revealed the nasal mucosa to be a deep red color (80) with 3 to 4 plus swelling, secretion and obstruction.

without nasal complaints for more than 3 years. The coincidence of situational threats and nasal disturbances in this patient is illustrated graphically in Fig. 7.

In many of the subjects studied the nasal changes were ultimately associated with chronic infection and polyp formation.

**General Comment and Formulation.**  
From the available data, samples of

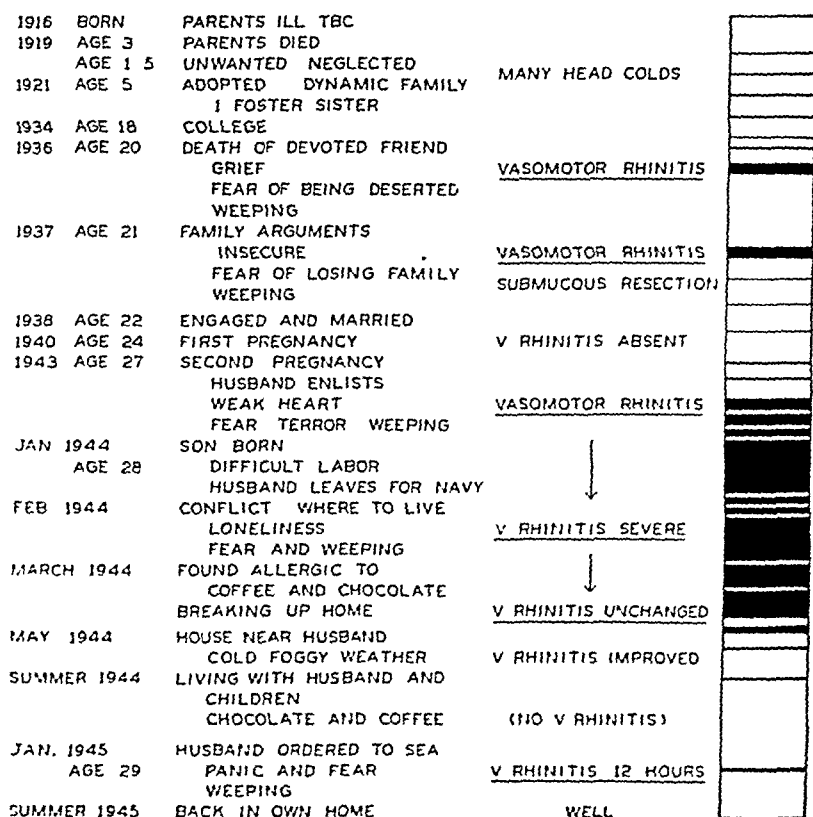


FIG. 7.—Life chart illustrating coincidence of situational threats and nasal disturbances in an insecure, anxious woman. The black bars at the right indicate the occurrence, duration and intensity of troublesome symptoms.

Eventually, during subsequent clinic visits, she was able to relate her fear of desertion to her childhood experiences and these fears to her symptoms. As this understanding was achieved, her nasal symptoms gradually subsided. By January, 1945, she was not only symptom free and effectively fulfilling her role as wife and mother, but her nasal structures were of average appearance—redness 30 to 40, 2 plus swelling, 1 plus secretion and no obstruction. She remained essentially

which have been presented in this communication, it would appear that the nasal hyperfunction characterized by hyperemia of the nasal mucosa associated with turgescence of the erectile tissues in the turbinates, swelling of the nasal mucosa, hypersecretion and obstruction to breathing, constitutes a part of a broad biologic protective

pattern of defense. Since respiration consists of an in and out circulation of air through the respiratory passages, the "shutting out" pattern of nasal hyperfunction thus involves equally a "shutting in". In effect, the individual diminishes his exchanges with his environment and limits the extent of his participation in the situation about him. Thus insulated, he takes in less and gives out less.

Subjects exhibiting this "shutting out—shutting in" pattern of non-participation have been studied<sup>13</sup> and were found to be defensive, insecure, sensitive and dependent individuals who talk with difficulty about relevant personal matters and seldom take positive steps to improve their state. They required a lively show of love and affection on the part of others but were unable to return significant amounts of sympathy, warmth and affection. In many who were deprived of devotion and tenderness in early life, events which threatened such emotional support in later life often induced an exacerbation of the defensive reaction of nasal hyperfunction. Such individuals were quick to react to threatening situations with feelings of intense humiliation and many of their attitudes and behavior patterns were designed to protect their sensitive feelings by "keeping the peace", "avoiding issues" and "doing for others". When their precarious security props were jeopardized, the content of the ensuing state of conflict included in addition to humiliation, intense resentment, frustration and guilt. They were often unable to admit or express feelings of hostility or anger but rather resorted to weeping or aggressive and desperate clinging to that which offered security.

Shutting out, neutralizing and washing away in the nose seems to imply defensive activity at the head end of the organism. During weeping the eyes

participate in the pattern. In some patients obstruction of the esophagus and in others constriction of the bronchi have been observed to occur in response to situations engendering conflict with anxiety and nasal hyperfunction<sup>14</sup>. The work of Faulkner and of Stewart Wolf<sup>6,35</sup> provides further convincing evidence that the bronchi and esophagus participate in the shutting out, non-participation pattern of defense. Thus, the respiratory apparatus and upper alimentary tract, the orbital and skeletal muscle structures of the head may act as a unit of function in shutting out, washing away and neutralizing an environment that is literally or symbolically noxious.

The pattern of nasal hyperfunction with hyperemia, swelling, hypersecretion and obstruction, is effective in keeping out of the body dust and irritant gases. It is less effective, however, in protection against blows to the head or situational threats involving interpersonal relations, such as hostility of a parent or marital partner. Indeed, if prolonged, the pattern itself may lead to distress in addition to that arising from a threatening life situation.

Hyperemia, hypersecretion and swelling occurring in a mucous membrane that is already hyperfunctioning can produce pathologic tissue changes. The edematous and chronically inflamed hyperfunctioning nasal mucosa can no longer tolerate or deal adequately with the insults of such noxious agents as pollens or irritant chemical fumes without the advent of additional hyperfunction of sufficient magnitude to induce the signs and symptoms of a "vasomotor rhinitis" and additional tissue damage. Indeed, such an altered nasal mucous membrane soon becomes unable to tolerate the additional hyperfunction induced by such ordinarily innocuous assaults as cold atmosphere, cutaneous chilling, dust or bright lights without symptoms.



Furthermore, as with other ducts and cavities in the body, the presence of chronic obstruction and loculation of secretion in the nasal cavities may favor the invasion and growth of microorganisms. Once it has become established, the infective process can prolong the period of morbid changes in the nasal and paranasal spaces and lead to serious disease and incapacity which may persist long after the precipitating emotional conflict has been resolved.

It is not implied from these observations that all nasal disease stems directly from situations involving difficulties in interpersonal and social adjustments. There are certainly other major factors which set in motion the chain of events described. However, situational threats involving interpersonal and social adjustments occupy a position of importance and may modify the course of the morbid process regardless of the precipitating incident.

**Summary.** 1. Life situations productive of conflict with anxiety, hostility, guilt and feelings of frustration and resentment were commonly accompanied by nasal hyperfunction with hyperemia, swelling of the nasal mucosa, hypersecretion and obstruction to breathing in the nose.

2. There was also observed an associated pyogenic-like reaction with

an increase in the neutrophil and eosinophil content of nasal secretions.

3. Biopsy obtained under these circumstances revealed edema of the stroma, dilated vascular and lymphatic channels and hypersecretion of the mucous glands.

4. Cholinergic impulses to the nasal mucous membranes, probably transmitted by the greater superficial petrosal nerve, are responsible for the production of the nasal hyperfunction.

5. The pattern appears to represent an attempt on the part of the organism to protect itself by shutting out, neutralizing and washing away an environment that is literally or symbolically noxious.

6. Nasal pain of 2 types commonly accompanied the nasal hyperfunction: 1, a burning pain located in one or both nostrils; and, 2, a dull, aching pain deep under the bridge of the nose and often experienced over the zygoma, in and above the eye, in the temple, upper teeth and ear. Infection of the nasal or paranasal spaces was not a necessary prerequisite for pain.

7. When such a pattern is unduly sustained, pathological changes occur which give rise to or prolong troublesome symptoms and, especially when coupled with other noxious threats and assaults, become important to the pathogenesis of chronic nasal disease.

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# SERIAL DETERMINATIONS OF PROTHROMBIN ACTIVITY IN PREGNANCY AND THE PUERPERIUM

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VARIOUS investigators have found an apparent increase in the prothrombin activity of blood under certain conditions. By means of the 1 stage assay method of Quick,<sup>11</sup> shortened prothrombin times of whole plasma, and more consistently, of diluted plasma, have been reported to occur during the post-operative period,<sup>14</sup> in the course of thrombophlebitis,<sup>15</sup> following coronary occlusion,<sup>10</sup> in the early stage of infectious hepatitis,<sup>12</sup> and after the administration of xanthine derivatives<sup>13</sup> or large doses of vitamin K preparations.<sup>18</sup> Prothrombin assay in pregnancy, by either the 1 stage method or the 2 stage method of Warner, Brinkhous and Smith,<sup>20</sup> has produced conflicting results. Using the 1 stage method, Brambel and Loker,<sup>1</sup> and Norris, *et al.*<sup>7,8</sup> noted acceleration of the prothrombin time, mainly in plasma diluted 1 to 4 and 1 to 8, in parturient women at the time of delivery. Field, Overman and Baumann<sup>4</sup> reported similar findings in rats during the last week of pregnancy, and also noted increased resistance to the prothrombinopenic effects of Dicumarol in pregnant and lactating rats. In studies of pregnant women at delivery, using the 2 stage prothrombin assay, Shettles, Delfs and

Hellman<sup>16</sup> found variable results, with the majority showing an increased prothrombin content; Javert and Moore,<sup>5</sup> in a similar investigation, noted reductions below normal in almost all their cases. Thordarson,<sup>17</sup> whose method resembles the 2 stage assay, found a gradual rise in plasma prothrombin content during the course of pregnancy and a decrease to normal levels after the first week post-partum. Of his 112 cases serial determinations were done in only a few. In the present study, changes in prothrombin activity during pregnancy and the puerperium were observed by performing serial estimations on individual patients.

**Method.** A total of 277 prothrombin determinations was done at various intervals on 62 clinic patients; 3 to 10 determinations (average, 5.8) were carried out in each of 41 women, and 1 to 4 determinations in each of the remaining 21 women. The method used was the 1 stage prothrombin assay of Quick, with modifications introduced by Link and Shapiro; the determinations were done on 12.5% saline-diluted plasma as well as on whole plasma. The details of the method were identical with those previously outlined, and the values for a control group was determined.<sup>2</sup> The range of normal values is indicated for both whole and 12.5% diluted plasma by the broken lines in Fig. 1.

**Results.** The data are outlined in Fig.

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1. A consistent trend is evident in the diluted plasma prothrombin times of the group as a whole; there is progressive shortening below the normal range, from the third month of pregnancy on, with shortest times appearing in the first few days post-partum. Values obtained several months post-partum were uniformly slightly elevated above normal. The same trend is present in

delivery, however, the whole plasma prothrombin times are prolonged. One patient with thrombophlebitis occurring in the first week post-partum and 2 with definite histories of phlebitis in previous pregnancies (but not in the present one) showed no differences from the remainder of the group.

**Discussion.** The changes recorded here gain added significance because

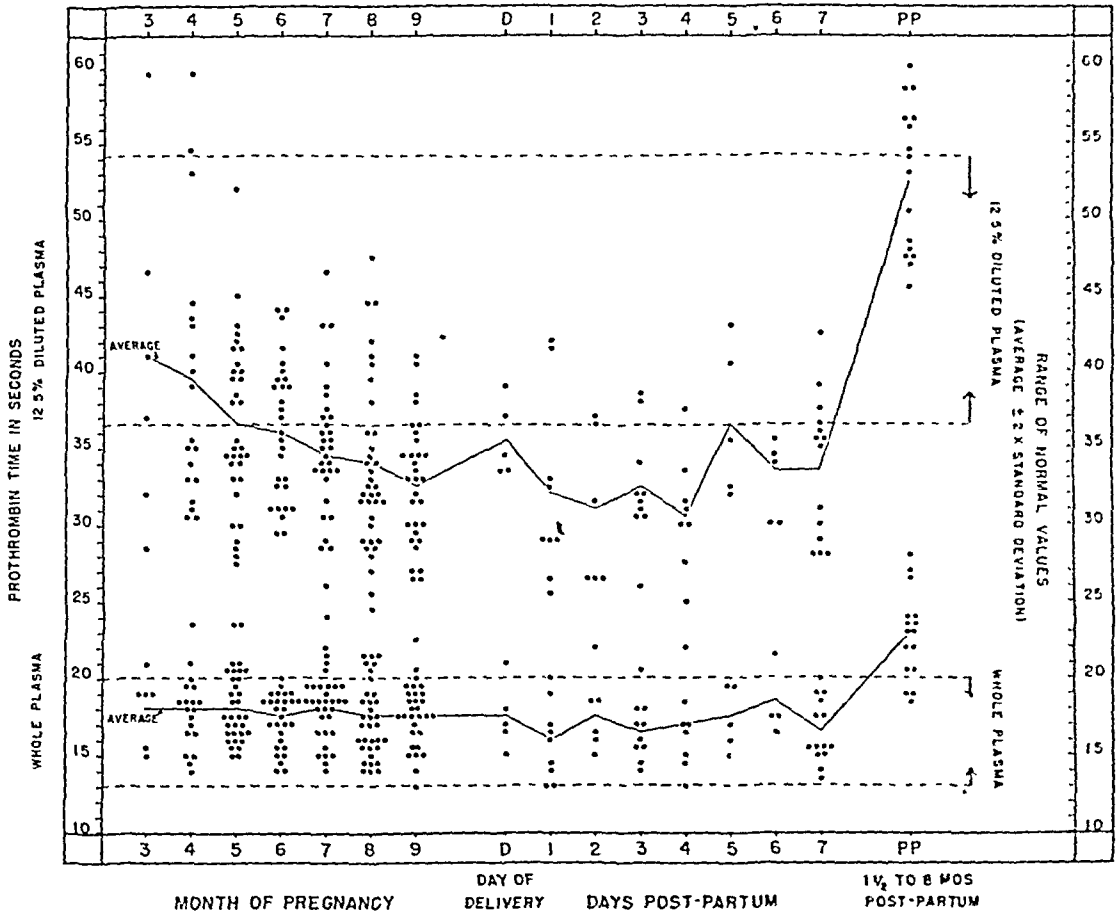


FIG. 1.—Prothrombin times in 62 cases during pregnancy and the post-partum period.

Dots represent individual determinations.

•=12.5% diluted plasma prothrombin time.

°=whole plasma prothrombin time.

the course of serial determinations on individual patients. The whole plasma prothrombin times show no significant alteration in the average values, although there are a few abnormally short times occurring in the latter months of pregnancy and in the first week post-partum. Several months after

of the plasma dilution which occurs toward the end of pregnancy and which of itself would lengthen the prothrombin time. While the mechanism of the further acceleration of the diluted plasma clotting time noted in the first few days post-partum remains to be elucidated, it may be due to the reduc-

tion in plasma volume which follows delivery.

It has been emphasized by several authors that an accelerated prothrombin time by the 1 stage method need not signify an actual hyperprothrombinemia, as variations in other factors in the complex coagulation process may influence the clotting times. Although the plasma fibrinogen concentration increases in pregnancy, and increased fibrinogen under certain experimental conditions may accelerate the prothrombin time (Nitshe, Gerarde and Deutsch<sup>6</sup>), this appears to be insufficient to explain the changes observed here. Further data are needed to clarify this relationship. A plasma activator factor for prothrombin conversion has been suggested (Fantl and Nance,<sup>3</sup> Owren,<sup>9</sup> Ware and Seegers.<sup>10</sup> Variations in this prothrombin activator could affect the results of the 1 stage method, and would tend to be more evident in diluted plasma. Antithrombin substances have been demonstrated in

plasma, but there is no data as to their effect on the results of the 1 stage prothrombin assay.

If the observed changes can be taken to signify an increased prothrombin "activity" of the blood, it appears that such an altered state of the coagulation mechanism can exist for a considerable time without resulting in clinical thrombosis.

**Summary.** In a group of 62 pregnant women, the 1 stage prothrombin determination on 12.5% saline-diluted plasma disclosed progressive acceleration of the clotting time beyond the normal range through the course of pregnancy, and lasting through the first week post-partum. At a later post-partum period, the prothrombin time was somewhat lengthened. The results were similar in individual cases in whom serial determinations were done to those of the group as a whole. No significant changes occurred in the whole plasma prothrombin time.

The authors are indebted to Miss Eleanor Perry for technical assistance in this investigation.

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# ANOMALOUS RIGHT PULMONARY VEIN ENTERING THE INFERIOR VENA CAVA: TWO CASES DIAGNOSED DURING LIFE BY ANGIOCARDIOGRAPHY AND CARDIAC CATHETERIZATION

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ANOMALOUS pulmonary veins are occasionally encountered during thoracotomy or at post-mortem examination. The usual anomaly is a variation in number from the expected paired bilateral vessels. Of more interest are anomalous points of entry of one or more pulmonary veins into sites other than the left atrium. These cases may be divided into those with partial shunt of the pulmonary venous return into tributaries of the right heart, and those with total shunt of the pulmonary venous return into the right heart. The latter condition, if uncomplicated by other severe cardiac anomalies, is dependent upon patency of the foramen ovale for life. Actually, very few if any individuals with total shunt survive beyond the first few months of life, and those few who have done so have had associated anomalies allowing free admixture of blood between left and right hearts.

In the literature, Brody<sup>3</sup> and others<sup>1,2,6,8,9,11,13</sup> report a total of 133 cases exhibiting partial (80 cases, 60.1%) or total (53 cases, 39.9%) drainage of pulmonary veins into tributaries of the right heart. The most frequent site was the superior vena cava (42 cases, 31.5%), next the right atrium (21 cases, 15.8%), and the left innominate vein (18 cases, 13.5%). Other sites such as the coronary sinus, a persistent left superior vena cava,

the inferior vena cava, the portal vein and the azygos vein accounted for the remaining 52 cases. In only 4 cases (3.0%) did drainage occur into the inferior vena cava.<sup>4,7,12,14</sup> Right pulmonary veins were found to be anomalous about twice as often as those on the left side. Drainage on the left usually was into the left innominate vein or into a persistent left superior vena cava, while on the right, the anomalous vein usually entered the superior vena cava or the right atrium.

Except for 3 cases observed by Brantigan<sup>2</sup> during pneumonectomy, none of the 80 reported cases of partial shunt of pulmonary veins into the right heart was diagnosed ante-mortem. Of the 4 reported cases of anomalous drainage of pulmonary venous blood into the inferior vena cava, none was diagnosed prior to death. We have observed 2 cases of this anomaly in adult males where modern methods made possible the diagnosis during life and without exploratory surgery. Their clinical reports follow.

**Clinical Abstracts.** CASE 1. A 27-year-old white male was referred for angiocardiology because of a crescent-like shadow in the right lower lung field, discovered on routine pre-induction chest roentgenogram in 1943. The patient was asymptomatic; past and family histories were negative. The physical examination was that of an apparently healthy adult male. There were no significant laboratory

findings. Conventional frontal roentgenogram of the chest (Fig. 1A) revealed asymmetry of the chest with the ribs more widely separated on the left. The heart was shifted slightly to the right and its right border appeared prominent. Curving downward through the lower right lung field was a band-like shadow which widened gradually as it descended, paralleling the right atrial

border. It then turned inward, becoming obscured at the right cardio-phrenic angle, at which point it measured 24 mm. in width. This shadow could not be identified on lateral examination and was probably superimposed on the cardiac shadow in that projection. An angiocardio-gram made in the frontal projection 3 seconds following the injection of contrast material (Fig. 1B) revealed some-

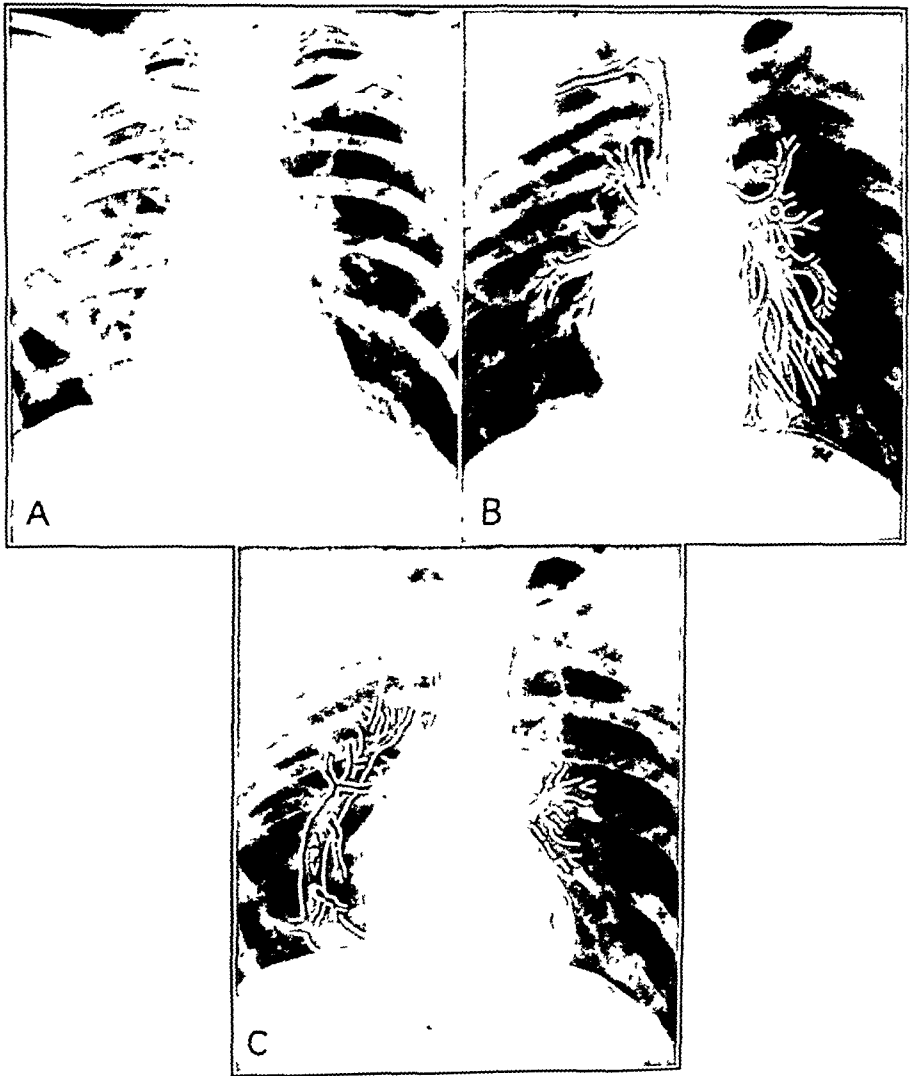


FIG. 1. CASE 1.—(A.) Conventional roentgenogram. Note prominent right heart border and crescent-like shadow in right lower lung field. Left interspaces are wider than those on right (B.) Angiocardio-gram (retouched), made the same day, film exposed 3 seconds after injection. Note slightly enlarged right ventricle, prominent pulmonary arteries on the left as compared to those on the right. Crescent-like shadow in right lower lung field is not opacified. (C.) Angiocardio-gram (retouched), made 8 seconds after injection. Left heart and aorta normal. Note opacification of crescent-like shadow, a common vascular trunk draining the right lung to the region of the inferior vena cava.

what enlarged right cardiac chambers. The pulmonary arterial bed was more prominent on the left than on the right side. A film made 8 seconds following injection (Fig. 1C) showed opacification of the left ventricle and the aorta. The left pulmonary vascular bed was unremarkable. The shadow in the right lower lung field was opacified and was seen to consist of a common vascular trunk which received converging vessels from the entire right lung, and which disappeared beneath the

diaphragm, apparently entering the inferior vena cava. This network of vessels did not resemble the usual pulmonary veins. The findings were interpreted as evidence of an anomalous common right pulmonary vein draining into the inferior vena cava.

CASE 2. A 41 year old Naval Lieutenant was admitted to the U. S. Naval Hospital, St. Albans, N. Y., for a diagnostic study occasioned by hypertension discovered upon routine examination. He was asymptomatic

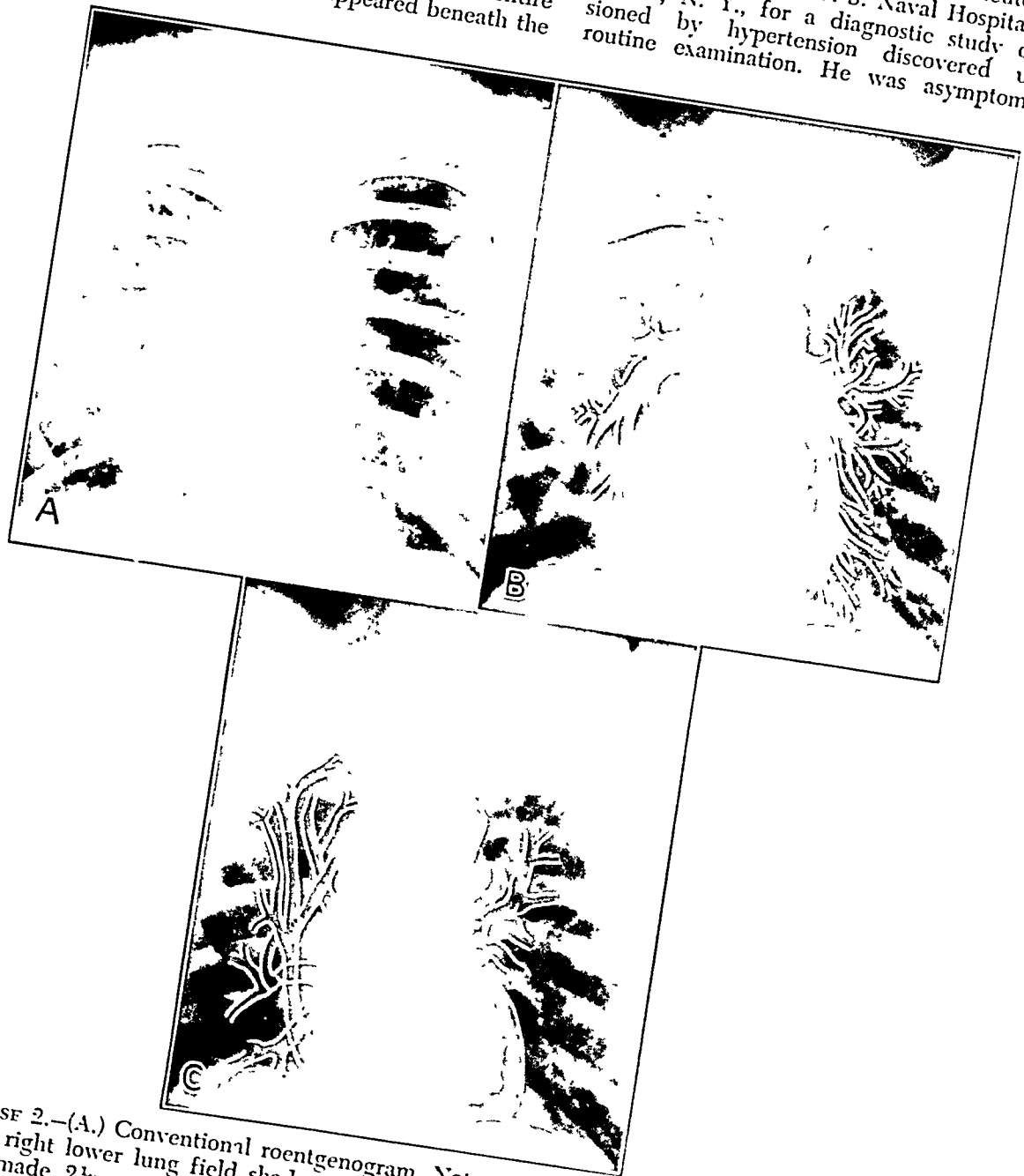


FIG. 2. CASE 2.—(A.) Conventional roentgenogram. Note prominent lower right cardiac border and vague right lower lung field shadows. (B.) Angiogram (retouched), made the same day, film made 2½ seconds after injection. Note slightly enlarged right heart, large left pulmonary artery and branches as compared to the right side. (C.) Angiogram (retouched), made 8 seconds after injection. Left pulmonary veins are normal. Note common vascular trunk apparently draining the entire right lung and disappearing in the region of the inferior vena cava.



save for mild headaches and fatigue, and the family and past histories were unremarkable. Physical examination revealed an apparently healthy white male save for the finding of blood pressure readings which ranged between 184/120 and 145/105. Laboratory studies were essentially negative save for a slight left axis deviation on electrocardiogram (thought due to the patient's hypertension). Conventional frontal roentgenogram of the chest (Fig. 2A) revealed a dorsal scoliosis with a shift of the heart towards the right. The right cardiac border appeared unduly prominent. On roentgenographic and fluoroscopic examination vague shadows described as exhibiting a "weeping willow effect" were noted in the right lower lung field and interpreted as suggesting a vascular anomaly. For this reason, angiocardiology was performed. A frontal chest roentgenogram was exposed 2½ seconds following the injection of a contrast substance (Fig. 2B) revealed slight enlargement of the right cardiac chambers. The left pulmonary artery was larger than normal and extensive pulmonary arterial vascularity was noted in the left lung field, while the right pulmonary artery was comparatively small and there was definitely diminished vascularity throughout the entire right lung field. A film exposed at 8 seconds after injection (Fig. 2C) revealed opacification of the left atrium, the left ventricle, the aorta and its brachiocephalic branches. A number of unremarkable pulmonary veins in the left lung field entered the left atrium in the usual manner. A network of opacified vascular shadows was seen throughout the right lung field. Individual vessels ran downward, converging at the level of the ninth posterior rib to form a common trunk 18 mm. in width. This vessel pursued a short downward course for 9 cm. where it curved close to the spine at the level of the eleventh rib and abruptly disappeared. A radiolucent area separated this vessel from the left atrium. The configuration of this network did not resemble that of the usual pulmonary veins. A diagnosis of anomalous right common pulmonary vein entering the inferior vena cava was made. Cardiac catheterization was subsequently performed. Oxygen content (vols. %) was determined on various samples of blood with results as follows: (1) Superior vena cava at junction of left and right innominate veins, 11.8, (2) at junction of superior vena cava and right atrium, 13.6, (3) right atrium, 14.6 and 14.4 (two samples taken), (4) inferior vena cava below level of diaphragm, 14.4. These findings were interpreted as showing the ingress of highly arterialized

blood into the inferior vena cava and its presence in the right atrium, a confirmation of the angiocardiological diagnosis. A slightly lower oxygen content in the right atrium than in the inferior vena cava would have been even more convincing evidence in this direction. Further pulmonary function studies are to be done upon this patient at a later date.

**Discussion.** Anomalous vascular channels causing drainage of pulmonary venous flow into the right heart or its tributaries have been reported in at least 133 cases. Total shunt of the pulmonary venous flow into the right heart is incompatible with prolonged life and is primarily of academic interest, both pathologically and embryologically. Partial emptying of the pulmonary veins into the right heart, however, is compatible with adult life (as in our 2 cases). Hughes and Rumore<sup>9</sup> estimate that less than 50% shunt to the right heart is compatible with normal life.

Both of our cases seem to bear out the hypothesis that a compensatory mechanism may effect a diminished function of the abnormally drained portion of lung. In Case 1 there was definite diminished volume of the right (affected) chest as compared to the left, suggesting that respiratory volume was less on the affected side. In Case 2, the evidence is even more convincing. The left pulmonary artery was larger than normal and the left or "good" lung showed hypervascularity of the pulmonary arterial tree. In contrast, the right pulmonary artery as seen angiocardographically was small in size and there was definite diminished vascularity of the pulmonary arterial ramifications, as compared to the expected normal and when contrasted with the unaffected side. These changes are probably similar to functional disuse atrophy and hypertrophy in general. In effect, such a patient has what might be referred to as a functional congenital pneumonectomy, since the oxygenated blood

leaving the right lung field is returned to the right heart without having been able to give up its oxygen to the tissues. In both cases, the right lungs, probably histologically unremarkable, are of no functional value to the patients.

Should the shunt be large, it would constitute a definite hazard to the patient, since the right heart would be (theoretically) forced to move a greater than normal minute volume of blood, while the left ventricle would move less than normal. Right ventricular hypertrophy would be expected and has been described.<sup>13</sup> Other undesirable factors may be present as well as a predisposition to right sided cardiac failure. Conant and Kurland<sup>5</sup> cite the case of a patient in whom infection of the anomalously drained lung ran a rapidly fatal course, possibly due to the decreased blood flow postulated above. Disease of the unaffected lung is a doubly serious situation since the anomalously drained lung is of no functional value. Since pneumothorax, atelectasis or surgical removal of the normal lung might bring on sudden death, since the surgical risk is similar to that in a patient with one lung, and since the risk of anesthesia is greater, thoracic surgery should be carefully evaluated.

Extensive pulmonary function studies on individual patients will be necessary in order to evaluate possible therapy for patients such as those reported above. Surgical restoration of the normal anatomical relationships, the ideal solution, would appear to be a more difficult and drastic procedure than is warranted. Similarly, pneumonectomy would seem to be indicated only in the presence or imminence of right heart failure. This is in contrast to the case of arteriovenous fistula of the lung, a more common and probably a more

serious condition wherein lobectomy or pneumonectomy is indicated.<sup>10,15</sup> At present, in the absence of criteria for pneumonectomy, conservative management will suffice. It would seem advisable to observe such patients routinely in an attempt to reduce the incidence of pulmonary infection. Patients in whom anomalous vessels drain pulmonary returning blood into tributaries of the right heart from part or all of one lung only, and in whom the condition has produced definite evidence of right sided cardiac strain would seem logical candidates for pneumonectomy. Combined bronchosprometry and cardiac catheterization can be expected to afford much valuable information still lacking.

The diagnosis of anomalous pulmonary veins may be made during life by angiocardiology and confirmed by cardiac catheterization. The findings by catheterization alone resemble those of interatrial septal defect and the differential diagnosis of these two anomalies must depend upon other evidence in most cases. In both of the cases presented here, the clue to ultimate diagnosis was supplied by abnormal shadows of an apparently vascular nature seen in conventional roentgenograms. The thoracic surgeon can be expected to discover anomalous pulmonary venous drainage during thoracotomy in rare cases. Angiocardiology is the most valuable means of diagnosis.

**Conclusions.** 1. Anomalous drainage of pulmonary veins into the right heart or its tributaries has been discussed from the standpoint of the existing literature, the anatomical findings, the functional abnormalities and the practical considerations referable to certain of these cases.

2. The functional changes consist of: (1) an increased right ventricular output (as compared to the left ventricular output and to a normal right

ventricular output), with secondary right ventricular hypertrophy, (2) compensatory increase of pulmonary arterial flow to the unaffected areas of lung and apparent diminution of blood flow to the abnormally drained areas, (3) comparative functional inactivity of the areas so drained.

3. Two instances of drainage of pulmonary veins from the entire right lung into the inferior vena cava have been presented. These cases were diagnosed during life, utilizing angiocardiology and cardiac catheterization, an achievement not, to our knowledge, previously reported.

Since this paper was submitted for publication, Johnson and McRae<sup>9a</sup> published the report of a patient in whom an anomalous right pulmonary vein apparently drained into the superior vena cava, the diagnosis having been made during life by the methods described in the present report. It is anticipated that further such case reports will be forthcoming.

Thanks are due Drs. John H. Dale and Roy W. Bonsnes for their assistance in connection with the cardiac catheterization study.

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# CLINICAL EVALUATION OF DIRECT WRITING ELECTROCARDIOGRAPHY\*

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UNTIL recently the action currents detected by all electrocardiographs commercially available have been recorded on sensitized paper in a camera unit. It has been necessary to develop and fix these tracings by the use of appropriate solutions before readings could be made. The inconvenience involved in this procedure has stimulated interest in direct writing electrocardiography so that there are now available on the market several electrocardiographs capable of transcribing the action currents upon a more or less permanent medium without the necessity of subsequently being processed photographically. Thus far the reliability of records thus obtained has been affirmed by the enterprises promoting the sale of these instruments but has not been confirmed by interested electrocardiographers.

In the present study no attempt was made to compare the several machines on the market or to determine the durability of the tracings. Its purpose was rather to evaluate one such direct recording machine† from the standpoint of the accuracy of the records immediately available in comparison with an instrument regarded as acceptable. To this end simultaneous records were obtained through a coupling

device transmitting the potentials to a direct writing electrocardiograph and to a standard amplifier type electrocardiograph§ in 25 subjects and through a similar device transmitting the potentials to a direct writing electrocardiograph and a standard string galvanometer type of electrocardiograph¶ in 10 additional individuals.

The coupling unit used for the combination of direct writer and amplifier type electrocardiograph consisted of a lead selector followed by a source of standardizing voltage, the combined output of the lead selector and standardizing circuit being impressed across both electrocardiographs connected in parallel. The coupling unit used for the combination of direct writer and string galvanometer avoided cross interference by converting the electrical impedance of the patient electrode circuit, normally 2,000 ohms. to a few ohms. This was accomplished with a battery-operated vacuum tube amplifier which employed cathode-follower action to impress across a low value resistor the signal applied to the input grids from the relatively high resistance patient electrode circuit. Connections to the electrocardiographs were made in a junction box where 1,000 ohm resistors were inserted in the patient leads of

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§ Stetho-Cardiette, Sanborn Company, Cambridge, Massachusetts.

¶ Simpli-trol, Cambridge Instrument Company, Ossining, New York.

both of the electrocardiographs to simulate the patient electrode resistance encountered in normal use. A lead selector switch was provided in the coupler unit and also a millivolt standardizing switch which served to synchronize all the recordings.

In order to insure that no distortion was introduced into the curves by the use of the coupling device a set of curves was then recorded in 3 individuals each attached directly, first to the direct writer, then to the string

not necessarily an indication of the accuracy of other machines on the market.

**Results.** In 25 subjects including individuals with normal cardiac mechanisms and various types of cardiac disturbances (anterior and posterior myocardial infarction, paroxysmal auricular tachycardia with block, auricular fibrillation, ventricular premature beats, etc.), the magnitude of the P. Q. R. S., and T waves and the duration of the P-R and QRS intervals, as recorded in

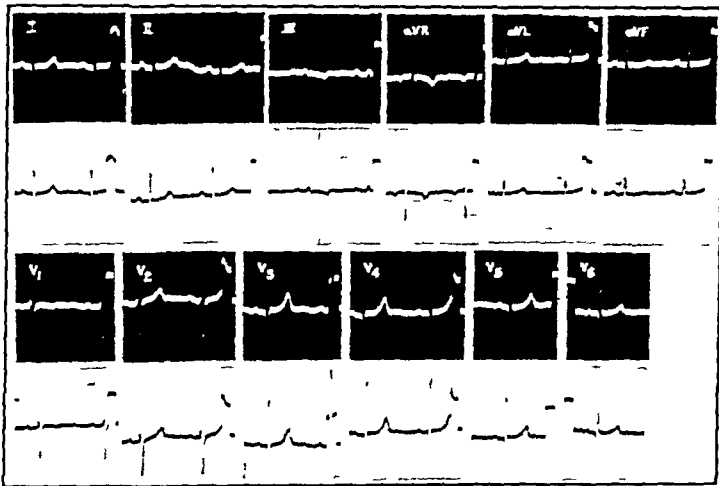


FIG. 1.—Simultaneous tracings taken from healthy young male with camera type amplifier electrocardiograph (white curve on black background) and direct writing electrocardiograph (black curve on white background) through coupling unit. No important differences are noted between the 2 sets of tracings. [This and subsequent figures have been reduced  $\frac{1}{2}$  and  $\frac{1}{4}$  from the original photographs submitted, without loss, however, of essential details. For detailed study the size submitted can be adequately brought back with a hand lens.—Ed.]

galvanometer, and finally to the amplifier type of electrocardiograph without the use of the coupler. Five sets of tracings were thus obtained in these subjects, 2 with and 3 without the use of the coupling device. Although it was impossible to compare identical complexes when the coupling device was not used, the intervals and deflections were then tabulated from what were taken to be representative complexes.

It is to be emphasized that tests made with one direct writing machine are

the direct writing and the vacuum tube (amplifier) camera type electrocardiograph were identical in the vast majority of cases. In very exceptional instances minimal and insignificant differences (0.01 second) were noted in the duration of the P-R or QRS intervals but in no instance did this constitute the difference between normal conduction on the one hand and auriculo-ventricular or intra-ventricular block on the other. In rare instances minimal and unimportant differences

were measured in the height of one or more of the deflections but no changes of importance, such as the loss of a prominent Q or S wave, or important shift of the electrical axis, were noted. In no instance was an elevation or depression of the RS-T segment detected with one instrument and not with the other. There was a superficial difference between the two sets of curves due to differences in the width of the baseline written by each of the machines. Representative comparative tracings are reproduced in Figs. 1 and 2, the former illustrating a normal cardiac mech-

times to standardize so that one millivolt produced just one centimeter excursion in each machine. When appropriate corrections were made for under- or over-standardization, slight differences were measured in the height of these deflections. The differences in the height of the R waves between the string galvanometer and the direct writer were more frequent and somewhat more pronounced than the differences between the direct writer and the vacuum tube type of electrocardiograph. In no case were Q waves or RS-T displacement found with one

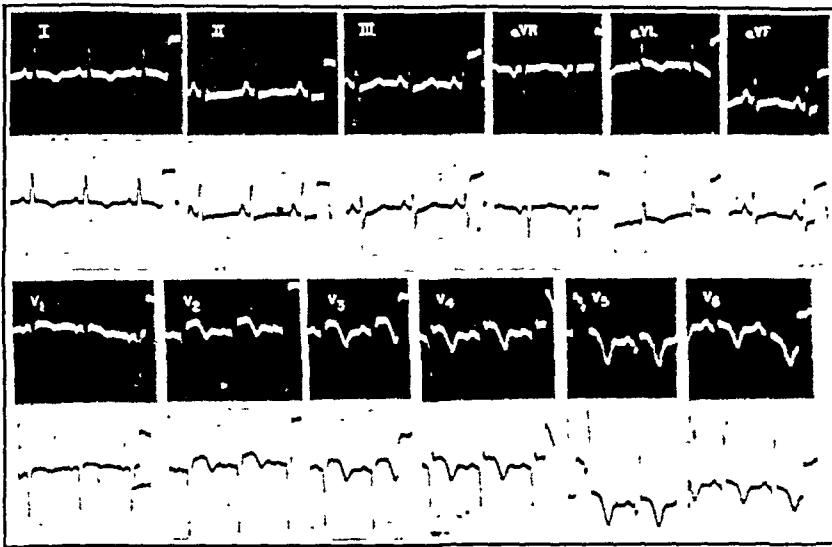


FIG. 2.—Similar tracings taken from 43 year old man with acute antero-septal myocardial infarction. No important differences between the 2 sets of curves.

anism and the latter an antero-septal myocardial infarction. It is to be noted that the R-R intervals were consistently 0.03-0.04 second shorter with the direct writer than the camera machine in Fig. 1 (slower rate) and 0.02 second shorter with the direct writer in Fig. 2. These changes are due to differences in paper speed and are not important.

In 10 additional individuals comparison was made of tracings simultaneously recorded with a string galvanometer and a direct writing electrocardiograph. With the coupling arrangement employed it was difficult at

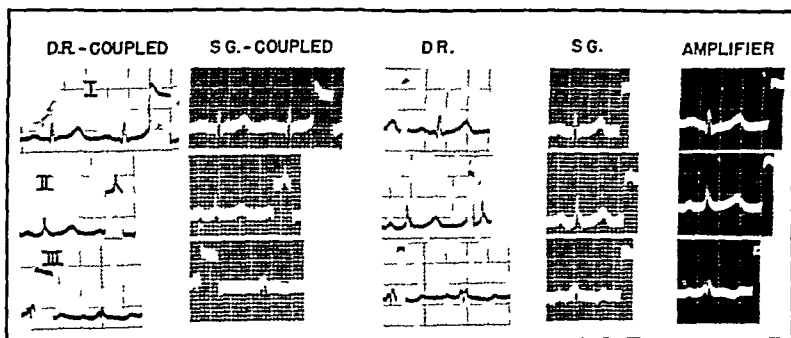
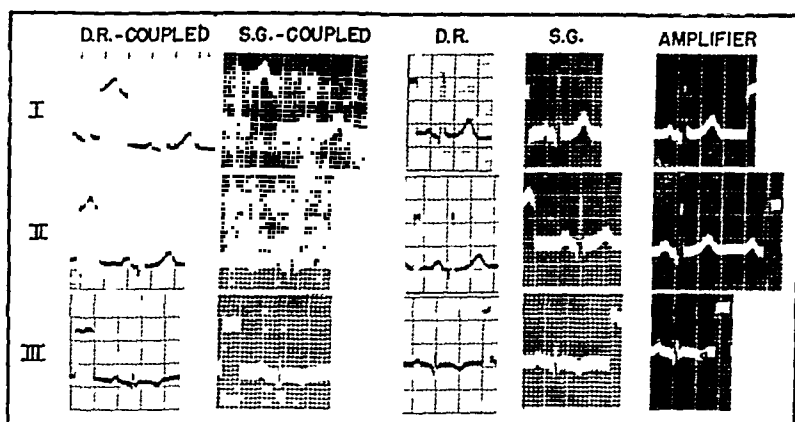
machine and not with another. In 2 individuals minute S waves were recorded with the string galvanometer and not with the direct writer. No important differences in electrical axis resulted from the slight differences detected in the height of the major QRS deflections.

There were also occasional differences in the duration of the P-R and QRS intervals, the difference usually being 0.01 second, rarely 0.02 second. When a difference was noted the shorter interval was usually recorded by the string galvanometer but oc-

casionally by the direct writer. When a shorter interval was recorded with the string galvanometer, this was due to the fact that the return limb of the R or S wave broke much more sharply with the isoelectric line in the string galvanometer than in the direct writer. At times notching on the downstroke of R, or an embryonic R, as recorded in the string galvanometer, was represented as a slur on the downstroke of R or as a broad, flat S by the direct writer. In no case in the present series did the differences recorded change the interpretation from normal conduction

to either auriculo-ventricular or intra-ventricular block.

**Conclusions.** A direct writing electrocardiograph operating on the vacuum tube principle was capable of immediately recording tracings faithfully duplicating those obtained with an acceptable camera type vacuum tube (amplifier) electrocardiograph. The occasional differences between tracings obtained with a direct writing and a string galvanometer type electrocardiograph were slight and clinically unimportant and in no case altered the interpretation made.



FIGS. 3 and 4.—Standard lead electrocardiograms in 2 healthy individuals (Subjects 34 and 35) obtained simultaneously with direct writer (1st vertical column) and string galvanometer (2nd vertical column) through coupling unit. The 3rd column shows tracings taken with the direct writer alone, the 4th with the string galvanometer alone and the 5th with an amplifier vacuum-tube electrocardiograph. The measurements obtained are given in Table 1.

TABLE 1.—COMPARATIVE MEASUREMENTS OF INTERVALS AND DEFLECTIONS RECORDED WITH DIRECT-WRITING, STRING GALVANOMETER AND AMPLIFIER TYPE ELECTROCARDIOGRAPHS

| Subject No. 34 |                             |             |             |             |          |          |          |          |           |           |          |
|----------------|-----------------------------|-------------|-------------|-------------|----------|----------|----------|----------|-----------|-----------|----------|
| Lead           | Machine                     | R-R<br>sec. | P-R<br>sec. | QRS<br>sec. | P<br>mm. | Q<br>mm. | R<br>mm. | S<br>mm. | R'<br>mm. | S'<br>mm. | T<br>mm. |
| I.             | Direct writer—coupled       | 0.62        | 0.12        | 0.10        | 0.8      | 1.4      | 11.4     | 0        | —         | —         | 3.0      |
|                | String galvanometer—coupled | 0.62        | 0.12        | 0.10        | 1.3      | 1.4      | 13.0     | 0        | —         | —         | 3.1      |
|                | Direct writer               | 0.70        | 0.12        | 0.09        | 0.9      | 1.3      | 12.2     | 0        | —         | —         | 3.1      |
|                | String galvanometer         | 0.67        | 0.12        | 0.08        | 0.9      | 1.8      | 11.7     | 0        | —         | —         | 3.0      |
|                | Vacuum tube (amplifier)     | 0.74        | 0.13        | 0.10        | 1.0      | 1.2      | 11.4     | 0        | —         | —         | 3.2      |
| II.            | Direct writer—coupled       | 0.70        | 0.14        | 0.07        | 1.0      | 1.5      | 9.9      | 0        | —         | —         | 2.2      |
|                | String galvanometer—coupled | 0.73        | 0.14        | 0.07        | 1.8      | 2.2      | 10.7     | 0.3      | —         | —         | 2.3      |
|                | Direct writer               | 0.70        | 0.14        | 0.07        | 1.5      | 1.6      | 11.0     | 0.3      | —         | —         | 2.3      |
|                | String galvanometer         | 0.65        | 0.14        | 0.08        | 0.9      | 2.7      | 11.6     | 0.9      | —         | —         | 2.1      |
|                | Vacuum tube (amplifier)     | 0.72        | 0.14        | 0.08        | 1.3      | 1.7      | 10.1     | 0        | —         | —         | 2.1      |
| III.           | Direct writer—coupled       | 0.60        | 0.14        | 0.08        | 0.9      | 0.5      | 0.3      | 1.0      | 1.5       | 0.5       | —0.6     |
|                | String galvanometer—coupled | 0.64        | 0.14        | 0.08        | 0.9      | 0.9      | 0.9      | 1.9      | 2.5       | 1.1       | —0.7     |
|                | Direct writer               | 0.70        | 0.14        | 0.09        | 0.6      | 0.4      | 0.1      | 1.8      | 1.8       | 0.5       | —0.6     |
|                | String galvanometer         | 0.66        | 0.14        | 0.09        | 1.0      | 1.0      | 0.4      | 2.1      | 3.2       | 1.0       | —1.0     |
|                | Vacuum tube (amplifier)     | 0.72        | 0.14        | 0.10        | 0.8      | 0.6      | 0†       | 1.6      | 2.0       | 0.7       | —0.7     |
| Subject No. 35 |                             |             |             |             |          |          |          |          |           |           |          |
| I.             | Direct writer—coupled       | 0.68        | 0.18        | 0.09        | 0.9      | 0.7      | 4.0      | 0.3      | —         | —         | 2.6      |
|                | String galvanometer—coupled | 0.69        | 0.18        | 0.09        | 0.8      | 1.3      | 4.0      | 0.7      | —         | —         | 2.1      |
|                | Direct writer               | 0.68        | 0.18        | 0.09        | 0.8      | 0.8      | 3.6      | 0.5      | —         | —         | 2.4      |
|                | String galvanometer         | 0.67        | ?           | 0.09        | 0.6      | 1.0      | 3.4      | 0.5      | —         | —         | 2.3      |
|                | Vacuum tube (amplifier)     | 0.80        | 0.18        | 0.10        | 0.6      | 1.0      | 3.1      | 0.5      | —         | —         | 2.2      |
| II.            | Direct writer—coupled       | 0.69        | 0.18        | 0.09        | 0.8      | 0        | 3.6      | 0        | —         | —         | 1.5      |
|                | String galvanometer—coupled | 0.69        | 0.19        | 0.08        | 1.2      | 0        | 5.0      | 0        | —         | —         | 1.7      |
|                | Direct writer               | 0.72        | 0.18        | 0.09        | 1.5      | 0        | 4.1      | 0        | —         | —         | 1.7      |
|                | String galvanometer         | 0.65        | 0.19        | 0.09        | 1.2      | 0        | 4.6      | 0        | —         | —         | 2.3      |
|                | Vacuum tube (amplifier)     | 0.78        | 0.19        | 0.10        | 0.9      | 0        | 4.3      | 0        | —         | —         | 4.1      |
| III.           | Direct writer—coupled       | 0.66        | ?           | 0.10        | 0.3      | 0        | 1.4      | 0        | 2.0       | —         | —0.4±0.4 |
|                | String galvanometer—coupled | 0.66        | 0.16        | 0.09        | 0.4      | 0        | 2.2      | 0        | 2.7       | —         | —0.4±0.4 |
|                | Direct writer               | 0.66        | 0.16        | 0.10        | 0.4      | 0        | 1.0      | 0.8      | 1.4       | —         | —0.5±0.3 |
|                | String galvanometer         | 0.67        | 0.16        | 0.09        | 0.4      | 0        | 1.5      | 0        | 2.2       | 0         | —0.5±0.6 |
|                | Vacuum tube (amplifier)     | 0.77        | 0.17        | 0.10        | 0.5      | 0        | 1.0      | 0        | 2.2       | 0         | —0.4±0.3 |

† "Embryonic" R wave



# THE COAGULATION TIME OF BLOOD IN SILICONE TUBES\*

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FREUND<sup>3</sup> showed many years ago that blood will clot much more slowly in a glass tube if that container is first coated evenly with paraffin. It was later noted by Gibbs,<sup>4</sup> who used the various wire loop methods of Inchley,<sup>7</sup> of Dale and Laidlaw,<sup>2</sup> as well as his own, that the type of metal and its state of cleanliness affected the coagulation time. These earlier observations have led to an attempt to explain the varying effects of contacting surfaces, particularly of glass on coagulation time.

The first thorough study attempting to correlate and control contacting surfaces was done by Lampert<sup>10</sup> in Germany and was reported in 1931. He measured the coagulation times in a wide variety of containers under various conditions; the materials included glass, paraffin, resin and other substances. He reported that coagulation times varied in a parallel manner with the surface tension of the blood in relation to the physical container. The substance with the least effect on surface tension was "athrombit," one of the resins, which at 37° C. gave an average coagulation time of about 30 minutes.

In 1942 Lozner and Taylor<sup>12</sup> used a plastic material, "lusteroid," in the form of tubes to determine coagulation times of plasma, and Tocantins<sup>14</sup> used

the same material for other studies of plasma. It was apparent that coagulation times were longer with this material. Kadish<sup>9</sup> employed this relatively nonwetttable surface for the measurement of the coagulation time of whole blood in an effort to determine whether abnormally shortened times were associated with certain diseases. He used syringes which had an oily protective coating.

Jaques and his co-workers<sup>8</sup> first reported on the use of the new material, silicone, a substance which can be used to coat glass. They found that it was easily applied as a liquid and when dried was smooth, nonwetttable, and increased the coagulation time of plasma at room temperatures. The plasma which in ordinary glass tubes formed a clot in 20 to 40 minutes in their experiment was still fluid after 2 to 4 hours in the silicone-coated tubes. These studies indicated that this substance was the most practical of any known for coating needle, syringe and tube, so that venipuncture followed by transfer of blood to a tube could be accomplished with a minimal disturbance of the blood.

Silicone is a clear liquid which does not appear to be changed by standing and may be kept in a capped bottle. It releases a pungent odor of vaporized hydrochloric acid on exposure to the

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air. We felt that this material might permit the development of a more accurate method of measuring coagulation time of whole blood. The main advantage, of course, would be the development of smooth, nonwetable surfaces by the coating of silicone. The material used in our work is one of a group of organosilicone compounds, made by General Electric, Schenectady, New York, labelled by them Dri-Film, no. 9987. Jaques and associates,<sup>8</sup> already referred to, worked with centrifuged blood. Since this probably produces significant changes in the coagulation mechanism, we decided to use whole blood without centrifuging for our study. The blood was kept at 37° C.

**Method and Procedure.** Relatively few materials were needed. We used 10 cc. syringes, test tubes 7 cm. long with an internal diameter of 8 mm., no. 19 and 20 needles. All glassware and needles were scrupulously cleaned and dried before using. The silicone was applied in the following manner. About 200 cc. were poured into a beaker which was placed under a hood. The plunger of each syringe was immersed so that the entire contacting surface was covered by the silicone. With the needle attached, the syringe was then filled and emptied in the silicone solution. To do this the plunger which had already been immersed in the silicone solution was used. The barrel was then filled and the silicone was allowed to run out of the barrel from the open end with the plunger removed so that all of this surface was also covered. Next the tubes to be covered were placed upright in a rack and were filled completely with silicone with syringes which at the same time were being coated. These tubes previously had been calibrated by making a mark on the outer surface at the 1 cc. level. The empty tube was filled with silicone which was allowed to remain in place for 2 or 3 minutes before being poured out again. The tubes were then washed thoroughly with distilled water, at which time pungent fumes appeared. Still wet, they were rinsed in dilute solution of ammonium hydroxide and rinsed again repeatedly in distilled water. The syringes were washed in the same fashion, using the same beaker throughout the whole procedure. Tubes and syringes were then baked for at least an hour at 100°

C. in a dry oven. The needles were left on the syringes during this whole procedure and were sharpened after the last rinsing while still wet. They were then placed in individual tubes and sterilized in an autoclave.

On removal from the oven, glass surfaces were seen to be covered by a very thin, smooth, transparent, greasy-appearing material. The syringes worked smoothly after repeated coatings (25 to 30 times in some instances). For the initial coating this whole process was repeated 2 or 3 times. Thereafter, the tubes were recoated once after each use. Syringes were not recoated as frequently and, after 5 or 6 coats were applied, were used for drawing blood about 5 times before a new coat was applied. The continuity of the surface in the syringe was examined by working the plunger and by looking at the surface in a good light. Needles were sharpened after every venipuncture. The silicone was returned to the large bottle after each use but when it became murky was discarded.

Experience with this technic showed us that many little details must be performed meticulously. For example, the needles often become plugged with silicone and have to be cleaned out. The groove in the metal ring of the syringe, where the needle is fitted and locked, may become filled with a gummy padding which can be removed with applicators. Often the small diameter of the syringe, through which the blood first flows on entering the syringe, became plugged with silicone which was removed mechanically.

Blood was drawn for tests from antecubital veins which were filled after occlusion above with a tourniquet. Only a clean venipuncture was used to provide a sample of blood. If one attempt was unsuccessful, the vein was not used but another vein was punctured. Enough blood was always drawn to leave 1 or 2 cc. in the syringe on the assumption that the first portion of the blood might contain more thromboplastin. This portion next to the plunger was not used.

One cc. of the blood was transferred from the syringe to a regular glass tube of the same size as those coated with silicone. Immediately thereafter 3 tubes coated with silicone were filled to the 1 cc. mark and placed in a water bath at 37° C. The remaining portion of the specimen of blood was left in the syringe, which was placed on the butt end of the plunger, so that it remained vertical. Ten minutes after blood was placed into the first glass tube another 1 cc. sample of blood from the syringe was placed into a fresh glass tube. Ten minutes later the same thing was done. Coagulation time of the

blood was measured in each of these tubes from the time the blood entered the glass tube. On a few occasions not enough blood was drawn to complete all of these tests. The blood in the uncoated glass tubes was kept at room temperature and a modified Lee-White<sup>11</sup> coagulation test was done. The tubes were tilted slightly every 30 seconds to determine the end point, which was reached when the blood would no longer flow even though the tube was inverted and tapped gently.

Blood in the silicone-coated tubes was tested as follows. The first tube filled was tilted gently every 5 minutes until signs of clot formation appeared, then every 2 minutes until the end point was reached; the second tube was undisturbed until clotting began in the first tube; it was then tilted every 5 minutes until clotting began and then every 2 minutes until the end point was reached. The

study were all done with the silicone-coated tube placed in a water bath at a temperature of 37° C. At this temperature it was possible to get relatively consistent end points.

**Results. Normal Subjects.** Studies were made on 50 normal individuals. These consisted of physicians, nurses, laboratory workers, college students and hospital employees. Their ages ranged from 18 to 65 years, and all were in apparently good health. There were 33 men and 17 women. The maximal time lost between the venipuncture and filling of tubes was 90 seconds, during which time the syringe was kept at a constant temperature by the body heat produced by the hand

TABLE 1.—SUMMARY OF COAGULATION TIMES IN MINUTES OF NORMAL SUBJECTS

| Method                         | No. | Mean  | Standard deviation | Standard error of mean | Range |
|--------------------------------|-----|-------|--------------------|------------------------|-------|
| <i>In glass</i>                |     |       |                    |                        |       |
| Immediately after venipuncture | 50  | 11.66 | 2.85               | 0.40                   | 5-19  |
| 10 minutes after venipuncture  | 46  | 10.6  | 2.95               | 0.44                   | 6-20  |
| 20 minutes after venipuncture  | 46  | 7.5   | 2.8                | 0.41                   | 2½-16 |
| <i>In silicone-coated tube</i> |     |       |                    |                        |       |
| Tube 1                         | 50  | 34.44 | 8.91               | 1.26                   | 25-72 |
| Tube 2                         | 50  | 36.42 | 8.44               | 1.19                   | 25-56 |
| Tube 3*                        | 50  | 38.58 | 8.20               | 1.16                   | 25-57 |

\* 88% had coagulation times in silicone-coated tube of 30 minutes or more.

third tube was undisturbed until clotting began in the second tube. Then it also was tilted every 5 minutes until clotting began, and every 2 minutes thereafter until the end point was reached. The end point was arbitrarily set at the complete cessation of flow when the tube was inverted. This produced a sharp end point, except in the longest time ranges when it was less definite. Coagulation times were recorded from the time the blood entered the syringe coated with silicone.

Early in the study attempts were made to measure the times at room temperatures, but some coagulation times were found to be as long as 2 or 3 hours. There was a wide variation in end points recorded in the 3 tubes which contained the portions of the same sample. Furthermore, these end points were not definite and in some instances a firm clot never formed. The results reported in this

in which it was grasped firmly and which covered the whole barrel.

Results of these studies are recorded in Table 1. Attention is first drawn to the readings in the silicone tubes. Since the third was the tube least handled and therefore least affected by undetermined variables, it was the one selected as the most accurate. This one was tilted only after evidence of beginning clot formation was seen in the first two. The average coagulation time was 38.58 minutes (standard deviation  $\pm$  8.2 minutes) in the 50 determinations. Times noted ranged from 25 minutes (2 individuals) to 57

minutes (1 individual). The difference in coagulation times between Tubes 2 and 3 was never more than 10 minutes, and averaged 2.2 minutes for the entire group. Interest in single measurements was largely on those near the lower limit for normal. It can be seen that coagulation times of less than 30 minutes in a silicone-covered tube were beyond the usual value for normal blood, and that anything less than 25 minutes might be regarded as abnormally rapid.

In Table 2 are recorded the results of repeated coagulation times in silicone-coated tubes on some of the

subjects already observed. Six had 3 tests each on different days. These showed considerable fluctuation and in 2 instances (Subjects 4 and 5) dropped to 30 minutes in one day. None dropped into the range of less than 30 minutes, and all excepting the two noted were well above the minimum established. Five subjects also had repeated tests done on the same day, the first early in the morning, the next just before lunch, the third in midafternoon. Fluctuations were again seen, with a coagulation time of 30 minutes in 1 instance (Subject 6), whereas all

TABLE 2.—REPEATED COAGULATION TIMES ON THE SAME NORMAL INDIVIDUALS

| Subject<br>or case                            | Date          | Age, yr.<br>and sex | Silicone-coated tube             |    |    |
|---|---------------|---------------------|----------------------------------|----|----|
|   |               |                     | 1                                | 2  | 3  |
|   |               |                     | Observations on 3 different days |    |    |
| 1   | Nov. 5, 1946  | 31M                 | 25                               | 30 | 34 |
|   | Jan. 20, 1947 |                     | 37                               | 39 | 47 |
|   | Feb. 11       |                     | 37                               | 39 | 39 |
| 2   | Jan. 8        | 26M                 | 30                               | 43 | 39 |
|   | Feb. 12       |                     | 37                               | 40 | 54 |
|   | Mar. 26       |                     | 39                               | 45 | 52 |
| 3   | Nov. 4, 1946  | 18F                 | 33                               | 37 | 41 |
|   | Feb. 14, 1947 |                     | 30                               | 30 | 32 |
|   | Feb. 15       |                     | 30                               | 39 | 35 |
| 4   | Nov. 20, 1946 | 21F                 | 35                               | 33 | 36 |
|   | Feb. 26, 1947 |                     | 25                               | 30 | 30 |
|   | Mar. 18       |                     | 39                               | 46 | 42 |
| 5   | Nov. 4, 1946  | 28M                 | 40                               | 40 | 45 |
|   | Nov. 11       |                     | 34                               | 30 | 30 |
|   | Feb. 12, 1947 |                     | 35                               | 41 | 40 |
| 6   | Jan. 2        | 28M                 | 30                               | 30 | 38 |
|   | Feb. 13       |                     | 30                               | 42 | 44 |
|   | Feb. 26       |                     | 32                               | 40 | 50 |
| Observations repeated 3 times on the same day |               |                     |                                  |    |    |
| 1   | 9:30 a. m.    | 31M                 | 37                               | 39 | 39 |
|   | 11:00 a. m.   |                     | 39                               | 42 | 42 |
|   | 4:00 p. m.    |                     | 35                               | 34 | 35 |
| 5   | 9:40 a. m.    | 28M                 | 52                               | 52 | 56 |
|   | 11:00 a. m.   |                     | 26                               | 35 | 35 |
|   | 5:00 p. m.    |                     | 35                               | 41 | 40 |
| 6   | 9:00 a. m.    | 28M                 | 30                               | 42 | 44 |
|   | 11:30 a. m.   |                     | 25                               | 30 | 30 |
|   | 3:55 p. m.    |                     | 32                               | 40 | 50 |
| 7   | 9:30 a. m.    | 19M                 | 32                               | 49 | 47 |
|   | 11:00 a. m.   |                     | 25                               | 43 | 46 |
|   | 4:00 p. m.    |                     | 25                               | 30 | 32 |
| 8   | 9:35 a. m.    | 20M                 | 59                               | 54 | 49 |
|   | 11:00 a. m.   |                     | 40                               | 44 | 45 |
|   | 4:05 p. m.    |                     | 35                               | 41 | 40 |

of the rest were well above the minimal point.

In the uncoated tubes which were filled with the first sample coagulation times varied from 5 to 19 minutes and averaged 11.6 minutes. All of these were done at room temperature. In

the tubes filled 10 minutes later the coagulation times ranged from 6 to 20 minutes and averaged 10.6 minutes in a total of 46 samples, with a standard deviation of  $\pm 2.95$  and standard error of mean of  $\pm 0.44$ . In the glass tubes to which blood was added 20 minutes

TABLE 3.—SPONTANEOUS, INTRAVASCULAR FORMATION OF CLOT

| Case                   | Age, yr.<br>and sex | Diagnosis                                 | Coagulation time, min. |                         |    |            |
|------------------------|---------------------|---|------------------------|-------------------------|----|------------|
|                        |                     |   | In<br>glass<br>tube*   | In silicone-coated<br>1 | 2  | tubes<br>3 |
| 9                      | 52M                 | Ac. thrombophlebitis                      | 11                     | 13                      | 17 | 23         |
| 10†                    | 72M                 | Chemical (sclerosing)<br>thrombophlebitis | 12                     | 45                      | 52 | 53         |
| 11                     | 64M                 | Ac. thrombophlebitis                      | 12                     | 22                      | 25 | 28         |
| 12                     | 53M                 | Ac. thrombophlebitis                      | 8                      | 23                      | 28 | 31         |
| 13                     | 40M                 | Multiple acute throm-<br>bophlebitis      | 11                     | 10                      | 12 | 12         |
| 14                     | 61M                 | Ac. thrombophlebitis                      | 9                      |                         | 20 | 26         |
| 15                     | 52M                 | Ac. thrombophlebitis                      | 12                     | 25                      | 24 | 24         |
| 16                     | 52F                 | Ac. thrombophlebitis                      | 11                     | 25                      | 25 | 28         |
| 17                     | 42M                 | Ac. thrombophlebitis                      | 10                     |                         | 20 | 23         |
| 18                     | 34F                 | Ac. thrombophlebitis                      | 8                      | 20                      | 23 | 23         |
| 19                     | 40F                 | Ac. thrombophlebitis                      | 12                     | 18                      | 22 | 23         |
| 20                     | 18M                 | Subsided thrombo-<br>phlebitis            | 14                     | 40                      | 44 | 44         |
| 21                     | 65M                 | Ac. thrombophlebitis                      | 14                     | 17                      | 18 | 19         |
| 22                     | 64F                 | Ac. thrombophlebitis                      | 15                     | 28                      | 30 | 32         |
| 23                     | 61F                 | Ac. thrombophlebitis                      | 19                     | 20                      | 20 | 20         |
| 24                     | 68M                 | Ac. thrombophlebitis                      | 13                     | 25                      | 25 | 29         |
| 25                     | 49M                 | Ac. thrombophlebitis                      | 10                     | 18                      | 25 | 32         |
| 26                     | 61M                 | Ac. thrombophlebitis                      | 11                     | 19                      | 23 | 25         |
| 27                     | 66M                 | Ac. coronary occlusion                    | 10                     | 42                      | 45 | 47         |
| 28                     | 37M                 | Pulmonary embolism                        | 12                     | 38                      | 38 | 38         |
| 29                     | 59M                 | Pulmonary embolism                        | 11                     | 10                      | 10 | 12         |
| 30                     | 60F                 | Pulmonary embolism                        | 18                     | 15                      | 16 | 20         |
| 31                     | 47F                 | Ac. art. occlusion<br>(2 days)            | 15                     | 48                      | 42 | 50         |
| 32                     | 66M                 | Ac. art. occlusion<br>(3 weeks)           | 10                     | 55                      | 45 | 53         |
| 33                     | 54F                 | Ac. art. occlusion<br>(1 day)             | 14                     | 14                      | 16 | 20         |
| 34                     | 66M                 | Ac. art. occlusion<br>(12 days)           | 9                      | 18                      | 20 | 22         |
| 35                     | 48F                 | Ac. art. occlusion<br>(6 hours)           | ?                      | 32                      | 35 | 30         |
| 36                     | 74M                 | Ac. art. occlusion<br>(4 weeks)           | 12                     | 30                      | 30 | 31         |
| Summary of data:       |                     |   |                        |                         |    |            |
| Mean                   |                     |   | 11.96                  |                         |    | 29.21      |
| Standard deviation     |                     |   | 2.68                   |                         |    | 11.27      |
| Standard error of mean |                     |   | 0.52                   |                         |    | 2.13       |
| Range                  |                     |   | 8-19                   |                         |    | 12-53      |
| Number of observations |                     |   | 27                     |                         |    | 28         |

† The precipitating factor was the injection of a sclerosing material into varicose veins.

\* Immediately after venipuncture.

after withdrawal, the coagulation times ranged from  $2\frac{1}{2}$  to 16 minutes with an average time of  $7\frac{1}{2}$  minutes (standard deviation of  $\pm 2.8$  and standard error of mean of  $\pm 0.41$ ). It should be noted that all testing was done by one person (HM), using as much as possible the same technic throughout. Of the first two, it can be said that there is no significant difference in the time recorded immediately after venipuncture and that noted 10 minutes later, with the blood kept in silicone containers.

*Acute Vascular Occlusion.* Twenty-eight patients who manifested some clinical evidence of a tendency to thrombosis were observed. These merit close and rather detailed examination. The data on this group are recorded in Table 3. On almost all of them only one study of coagulation time was possible because anticoagulant therapy was used as early as possible. Sixteen had acute thrombophlebitis, which involved veins of the leg. One of these (Case 13, Table 3) also had other veins involved. One patient had thrombophlebitis as a result of the injections of sclerosing solution for varicose veins and 1 patient had passed the active stage of thrombophlebitis, the onset having been 3 weeks prior to the time at which our test was made.

The 16 patients who had acute thrombophlebitis had coagulation times in silicone tubes which ranged from 12 to 32 minutes. For 3 (Cases 12, 22 and 25) of the 16 (18.8%) they were more than 30 minutes; for the others, 1 was only 29 minutes (Case 24), and 1 was only 12 minutes (Case 13), with the remainder lying between these extremes. The coagulation times of 8 of the patients were lower than any observed on the normal subjects. The most rapid, referred to before, was in Case 13 and this was a sample of blood taken from the 1 patient who died. Necropsy revealed that he had

carcinoma of the pancreas, complicated by thrombosis in legs, pelvis and abdomen.

Coagulation times in glass tubes at room temperatures on the same group of patients varied from 8 to 19 minutes. The shortest time was noted in Case 12 in which the silicone coagulation time was 31 minutes; the longest time was noted in Case 23 in which the silicone coagulation time was 20 minutes. In Case 10, the case of chemical thrombophlebitis and in Case 20 in which the onset of thrombophlebitis was 3 weeks previously, the silicone coagulation times were within the upper limits of those of the normal subjects.

One case of coronary occlusion and 3 of pulmonary embolism were studied. The patient who had the acute occlusion (Case 27) was so severely ill that he died 2 hours after admission to the hospital. Necropsy was not performed. His silicone coagulation time was 47 minutes. The 3 patients who had pulmonary embolism survived. Two of these had coagulation times in silicone tubes which were well below normal (12 minutes and 20 minutes) and 1 was in the range of normal (38 minutes).

Six patients suffered from sudden arterial occlusion in an extremity, from a few hours to 4 weeks previous to the time the test was made and all were having distress as a result of interference with their arterial circulation. Two of the 6 had silicone coagulation times clearly below normal (20 minutes and 22 minutes); one of these (Case 34) died several days after the test was made, and necropsy revealed thrombotic occlusion of the lower part of the abdominal aorta, whereas the other (Case 33) recovered. Three pursued uneventful courses. One (Case 31) showed no improvement in a week, at the end of which time the affected leg was amputated. The femoral and

popliteal arteries were occluded by thrombi.

*Chronic Occlusive Arterial Diseases.* There were 23 patients in this group. All came to the Mayo Clinic primarily for treatment of vascular disease. Coagulation times of this group are recorded in Table 4. Ten had thrombo-

utes) in the cases of acute thrombophlebitis.

Thirteen patients had arteriosclerosis obliterans. The silicone coagulation times of 2 of these 13 was less than 30 minutes; these 2 (Cases 51 and 57) were kept on dicumarol therapy, and 1 of them (Case 57) will be referred to

TABLE 4.—OCCLUSIVE ARTERIAL DISEASES: 23 CASES

| Case                                 | Age, yr.<br>and sex | In glass<br>tube <sup>a</sup> | Coagulation time, min. |                               | 3     |
|--------------------------------------|---------------------|-------------------------------|------------------------|-------------------------------|-------|
|                                      |                     |                               | 1                      | In silicone-coated tubes<br>2 |       |
| Cases of thromboangiitis obliterans  |                     |                               |                        |                               |       |
| 37                                   | 52M                 | 14                            | 25                     | 29                            | 38    |
| 38                                   | 62M                 | 14                            | 26                     | 35                            | 32    |
| 39                                   | 47M                 | 14                            | 35                     | 38                            | 39    |
| 40                                   | 49M                 | 15                            | 20                     | 23                            | 29    |
| 41                                   | 49M                 | 19                            | 20                     | 22                            | 29    |
| 42                                   | 48F                 | 10                            | 20                     | 27                            | 27    |
| 43                                   | 36M                 | 10                            | 25                     | 30                            | 34    |
| 44                                   | 38M                 | 15                            | 40                     | 35                            | 40    |
| 45                                   | 43M                 | 9                             | 25                     | 40                            | 40    |
| 46†                                  | 58M                 | 11                            | 30                     | 35                            | 35    |
| Cases of arteriosclerosis obliterans |                     |                               |                        |                               |       |
| 47                                   | 79M                 | 11                            | 82                     | 75                            | 72    |
| 48†                                  | 50M                 | 16                            | 32                     | 30                            | 35    |
| 49                                   | 74F                 | 15                            | 30                     | 37                            | 38    |
| 50†                                  | 60M                 | 11                            | 25                     | 38                            | 30    |
| 51                                   | 62F                 | 9                             | 22                     | 20                            | 23    |
| 52                                   | 58M                 | 11                            | 24                     | 28                            | 30    |
| 53                                   | 62M                 | 13                            | 32                     | 33                            | 34    |
| 54                                   | 56M                 | 14                            | 33                     | 33                            | 30    |
| 55†                                  | 79M                 | 13                            | 70                     | 70                            | 75    |
| 56                                   | 65M                 | 18                            | 25                     | 35                            | 35    |
| 57                                   | 48M                 | 10                            | 23                     | 27                            | 27    |
| 58                                   | 58M                 | 9                             | 35                     | 40                            | 42    |
| 59                                   | 63M                 | 9                             | 34                     | 41                            | 36    |
| Summary of data                      |                     |                               |                        |                               |       |
| Mean                                 |                     | 12.61                         |                        |                               | 36.96 |
| Standard deviation                   |                     | 2.93                          |                        |                               | 12.53 |
| Standard error of mean               |                     | 0.61                          |                        |                               | 2.61  |
| Range                                |                     | 9-19                          |                        |                               | 27-75 |
| Number of observations               |                     | 23                            |                        |                               | 23    |

\* Immediately after venipuncture.

† With diabetes.

‡ With gangrene.

angitis obliterans; 3 of these had silicone coagulation times of less than 30 minutes and 1 of them (Case 42) was a woman. The most rapid coagulation time in silicone-coated tubes in this group (27 minutes) was considerably longer than the most rapid (12 min-

more extensively in a later paper. He exhibited clinically a thrombosing tendency. The rest of this group of 13 patients had silicone coagulation times within the range accepted as normal.

Comment. Bizzozzero,<sup>1</sup> when first describing the platelet, postulated that its

disruption and the simultaneous disruption of the leukocyte by various foreign substances precipitated coagulation. Gratia<sup>6</sup> agreed with the explanation that glass caused a disruption of the platelets which released a thromboplastic material, thus initiating a clot. He also stated that certain colloids of the blood were changed by the action of glass and contributed to the same mechanism. The destruction of platelets by contacting surfaces has been commonly considered responsible for this phenomenon. Pickering and de-Souza<sup>13</sup> suggested that fibrinogen has a colloidal protective coat, which is not removed so rapidly in paraffin-lined vessels, but is rapidly dissolved by the action of glass. Gortner and Briggs,<sup>5</sup> who in 1928 measured the electrical charge of various materials, felt that it was possible in theory that glass absorbs positively charged constituents of the blood to its surface in sufficient concentration to initiate coagulation, but they were not actually studying clotting mechanisms. More recently, Lozner and Taylor<sup>12</sup> found that platelet-free centrifuged plasma was capable of clotting, that it acted in a manner similar to platelet-rich plasma. They stated that the effect of foreign surfaces on blood coagulation is essentially independent of the platelet. In the study of Jaques,<sup>8</sup> previously referred to, a poor correlation was found between the number of platelets and the coagulation times and this lent support to the conclusions of Lozner and Taylor.<sup>12</sup>

*Tocantins*<sup>14,15,16</sup> has shown that blood contains an antithromboplastic substance, anticephalin. He found that when this substance was removed from plasma the clotting mechanism was greatly hastened on subsequent addition of thromboplastin. Various silica substances absorbed the anticephalin, and glass was one of these substances.

He attributed the different actions of lusteroid, paraffin, and glass tubes to the variable removal from the plasma of this anticephalin.

It is obvious that a silicone coating on glass inhibits some factor or factors which tend to hasten clot formation *in vitro*. By the same token it is seen that the method involved still introduces environmental influences which disturb the equilibrium needed to keep the blood in its physiologic fluid state. The difference between rapidity of coagulation in glass and in silicone is an indication of the relative crudeness of the test when glass is used; at room temperature this is the difference, in some instances, between a coagulation time of 10 minutes and one of 2 hours or more. One of the primary objects in using such a modification in technic is to discern fluctuation in the normal and from the normal. Contact with glass appears to throw the coagulation system into such violent disarray that more sensitive variations are submerged. Thus, only the most gross abnormality is adequately reflected when the glass tube method is used. It is, therefore, possible that some of the differences in readings from one individual to the next, and in the same subjects, in silicone-coated tubes are the result of accurate measurements and that the same fluctuations that the body exhibits throughout, in other functions, are present in the coagulability of the blood.

It is also likely that a significant error remains even when tubes and syringe coated with silicone are used. A venipuncture, for example, introduces some thromboplastin into the specimen, and it is not known how much this is, or how evenly it is diluted throughout the specimen. No matter how carefully this part of the test is done the exact conditions cannot be consistently repeated. In a series of silicone-coated tubes containing portions of the same specimens



of blood there is a greater difference in end point from one tube to the next as the total times get longer. Probably this increasing error is contributed to greatly by the thromboplastin. Before the water bath was used, and end points were still not definite at the end of 2 or 3 hours, the variation between tubes was as much as 45 to 60 minutes in some instances, although they were portions of one sample of blood. Deliberate introduction of a flaw, such as dirt on the silicone surface, returned the coagulation time to that found in uncoated glass.

The coagulation times in silicone-coated tubes, recorded in Table 1, indicate the effect of gentle tilting every 5 minutes. Although the tilting was done only 5 or 6 times more than in the next tubes, in many cases the clot was formed more quickly. An attempt to eliminate the effects of difference in tilting might be worth while. A mechanical device could conceivably replace manual tilting and thereby increase consistency.

The range of results seen in repeated observations on the same subjects probably represents both normal fluctuations and technical factors. The shortest times produced remained on the low border of the previously established range of normal.

The maintenance of fluidity of the blood in the syringe, left at room temperature, is worthy of attention. It can be concluded that any change in potential coagulability up to 10 minutes is not reflected in the tests done in glass tubes. It is probable that some disruption of platelets is occurring, but this is not marked enough to become apparent by the usual tests. This indicates that there may be some desirable latitude in time spent preparing slides for various studies of morphology if the blood is kept in silicone-coated containers. This could be improved even further, then, if the slides used were

also coated and such studies may produce some interesting results.

Also worth noting was an apparent difference in the physical character of the clots formed. The normal subjects, especially those who had blood which clotted in the longer time ranges, produced clots which formed the usual clear end point, but which slid out of the silicone tube in a uniform mass, keeping the shape produced by the contour of the tube almost intact. The remaining drops could be washed away easily. At the opposite extreme was the familiar picture of the clot in the glass which is irregular, tenacious, and has to be removed with a brush. If the silicone-coated tubes were allowed to sit for a few hours, the clot lost its adhesiveness entirely and was virtually floating free in the serum produced around it by retraction. In cases in which the blood clotted more rapidly in the silicone tubes, such as those in Table 3, a clot appeared to adhere more firmly to the wall of the tube although never as markedly as in glass. It is possible that the physical nature of an intravascular thrombosis is also variable, and the concomitant clinical pattern is affected thereby.

The findings on those patients who had acute thrombophlebitis were of particular interest to us. Only 18.8% of this group had silicone coagulation times of 30 minutes or more in contrast with the normal subjects, 88% of whom had silicone coagulation times of 30 minutes or more. It is reasonable to believe that this apparent hypercoagulability contributes significantly to the clotting which occurs as an integral part of the disease. It would be better if these determinations could also be made before the disease makes its presence noted to be absolutely sure that the changes in coagulation time precede the thrombophlebitis. It also should be noted that some of the patients had coagulation times in normal

ranges, despite the presence of definite thrombophlebitis, and that the data for groups of patients who had thromboangiitis obliterans and arteriosclerosis obliterans revealed coagulation times similar to those of the normal subjects. This further substantiates the clinical evidence that no single factor is responsible for the pathologic changes that occur in these diseases.

The method used for silicone coagulation times at present is tedious, especially when results are in the longer time ranges. Its greater accuracy is important when it is valuable to know more about coagulation, whether it is the sole cause of an illness or one of the causes. It would be helpful if some mechanical determination of the end points could be devised to obviate the laboriousness of the tests and the personal factors. If one is interested in demonstrating more rapid times the silicone-covered tubes containing blood could be placed in a water bath, to be checked only 4 times, at the end of 15, 20, 25 and 30 minutes. By this method definite, borderline, and absence of hypercoagulability could be determined.

**Summary.** A means of measuring coagulation time in containers coated

with silicone has been described. Normal times in silicone-coated tubes, established on 50 subjects, ranged from 25 to 57 minutes, with an average of 38.58 minutes. Eighty-eight per cent had coagulation times of 30 minutes or more; therefore 30 minutes is regarded as the usual lower limit of normal.

The effect on the coagulation time of leaving the blood in syringes coated with silicone before it was transferred to glass tubes for testing was recorded on the same subjects. No significant difference was recorded between coagulation times immediately after venipuncture and those obtained on a portion of the same sample left in a silicone-coated syringe for 10 minutes.

Patients with clinical evidence of thrombosing tendencies have been studied and abnormally rapid silicone coagulation times seen in a significant number of them. The patients with acute thrombophlebitis had times of 30 minutes or more in only 18% of those studied; 39.3% of all patients who had spontaneous intravascular clotting had coagulation times of 30 minutes or more.

The silicone coagulation times of nearly all of 23 patients who had occlusive arterial diseases were in the normal range.

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# THE COAGULATION TIME OF BLOOD IN SILICONE TUBES IN PATIENTS RECEIVING DICUMAROL\*

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IN THE previous paper<sup>3</sup> we presented data derived from the use of a method for measuring coagulation time of blood in silicone-coated containers. Studies were done on normal subjects and on patients who demonstrated clinically some increased tendency to form intravascular blood clots. Normal coagulation time with this technic, in which the temperature was maintained at 37° C., was from 25 to 57 minutes, with an average time of 38.58 minutes. The technic was found to be dependable in that the end points were clear-cut and the results were reproducible under the variety of conditions outlined in that paper. It was also shown that most patients with acute thrombophlebitis had silicone coagulation times which were abnormally low or at the lowest limits of normal and that this was also true for some of the patients with acute arterial occlusion and with thromboangiitis obliterans.

In the present study it has been our aim to apply the same method of measuring coagulation times to a group of patients receiving Dicumarol. Published reports<sup>1</sup> clearly show that in prothrombin deficiency there is no satisfactory correlation between coagulation times of whole blood in glass tubes and prothrombin times when the coagulation times are determined by the conven-

tional methods and the prothrombin times are measured by either the Quick method or the 2-stage method.

**Procedure.** Thirteen patients who were receiving Dicumarol were studied. These patients were in two general groups: (1) those in whom intravascular thrombosis had developed; (2) those postoperative patients who had not had intravascular thrombosis but who were treated prophylactically to prevent venous thrombosis and pulmonary emboli. All were given 300 mg. of dicumarol for the initial dose, and were then given either 100 or 200 mg. on any day in which the prothrombin time was less than that time corresponding to the time for 20% normal prothrombin activity (35 seconds in this laboratory).

The prothrombin time was determined by the routine method of this laboratory, the procedure being a modification of the Quick technic.<sup>2</sup> Normal prothrombin time (100% prothrombin activity) was 17 to 19 seconds. It was determined on every day of the study. The sample of blood was drawn in the morning, all of it being taken into a silicone-coated syringe, portions of this specimen being used for both prothrombin time and whole blood coagulation time.

**Results.** Figs. 1 through 4 are representative graphs with curves of prothrombin times plotted to compare with those representing silicone and glass coagulation times. Generally, the curve of the silicone coagulation times corresponds to that of the prothrombin times.

\* Abridgment of part of thesis submitted by Dr. Margulies to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

In each individual studied there were changes in the same direction in the prothrombin time and the silicone coagulation time. As the prothrombin time got longer a similar change occurred in the silicone coagulation time, and the reverse was also true. These changes were not always simultaneous; that is, in some patients the rise in the coagulation time appeared the day after the rise in prothrombin time (Figs. 3 and 4). One patient had a rise and fall in prothrombin time the first 3 days which was not reflected at all in the

coagulation times, which went up only with the secondary rise of prothrombin times. To repeat, however, changes in the silicone coagulation times corresponded to changes in prothrombin times in each individual in a very definite manner, as is best illustrated in the figures, but the changes were not always simultaneous.

The data were also examined for all of the subjects at once, rather than for each individual separately. It was found that no correlation existed if all of the prothrombin times were plotted

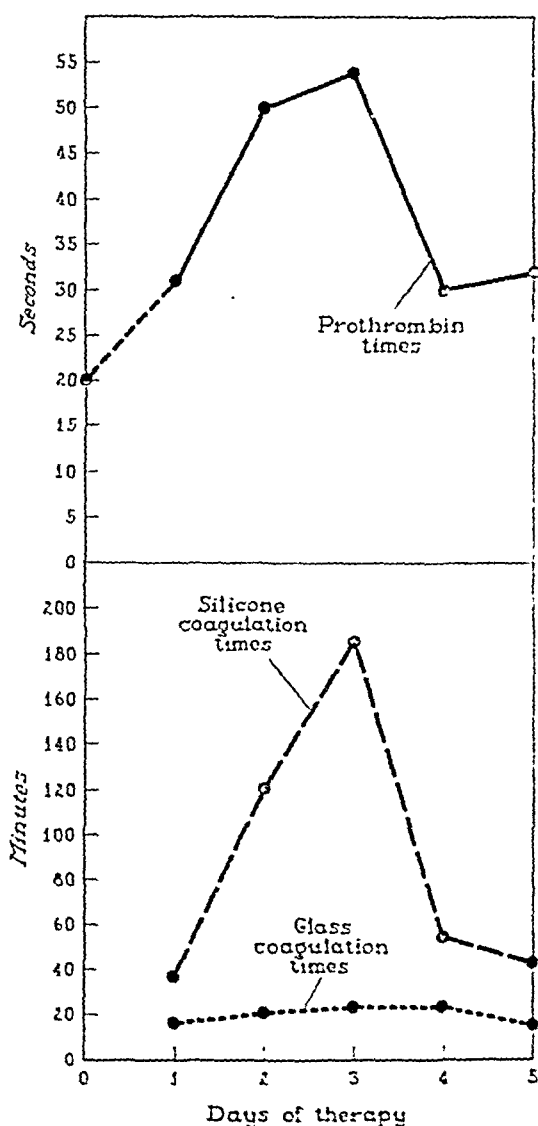


FIG. 1.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Female patient, aged 32 years, receiving Dicumarol prophylactically beginning 3 days after total abdominal hysterectomy.

against all of the silicone coagulation times. Stated differently, the same prothrombin time in different individuals was associated with widely different coagulation times; furthermore, a change of the same magnitude in prothrombin time on 2 successive days was accompanied by changes of variable magnitudes in the silicone coagulation times on those days. For example, on the fifth day of therapy Patients 1 and 3 had prothrombin times of 32 and 33 seconds, respectively; the corresponding silicone coagulation times were 42 and 120 minutes. Patient 11 had a prothrombin time of 34 seconds on the eleventh day of therapy, and Patient 13 had one of 33 seconds on the seventh day; corresponding silicone coagu-

lation times were 28 and 52 minutes respectively. This last patient was of unusual interest in that he had a high tolerance, apparently, for Dicumarol. It took 7 days and a total intake of 1,000 mg. of the drug to get his prothrombin time up to 33 seconds. Despite the failure to reach the clinically desirable level of 35 seconds, the coagulation time became abruptly longer when the prothrombin time was only at 22 seconds and maintained a level twice as long as its starting point, to which it returned when the prothrombin time dropped back to 18 seconds. Between the third and fourth day of treatment the prothrombin time lengthened by 2 seconds, with simultaneous lengthening of silicone coagulation time

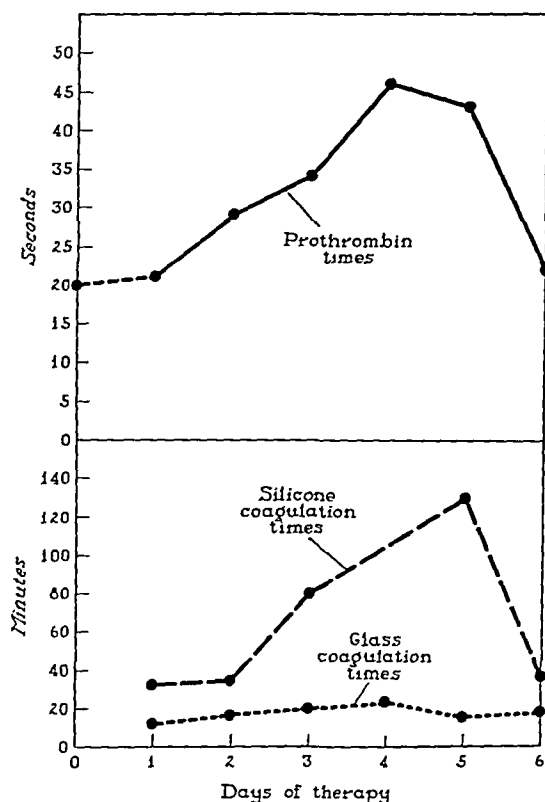


FIG. 2.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Female patient, aged 65 years, receiving Dicumarol prophylactically beginning 3 days after total hysterectomy.

of 15 minutes. Patient 11 on the same days had a lengthening of prothrombin time of 18 seconds with only a 10 minute prolongation of the coagulation time.

It should be emphasized again that, as the silicone coagulation times became longer (more than 50 to 60 minutes), the degree of error appeared to increase, and it is likely that variations in actual times in the longer ranges cannot be taken at face value. The difference between a coagulation time of 95 and 120 minutes may represent mostly the error factor. This error may be due to the variable amounts of thromboplastin present.

Recordings were also made for the times in glass tubes which were not coated, and these were relatively insen-

sitive to prothrombin changes compared with the silicone tubes. In some instances the anticipated change was reversed.

**Comment.** These data, derived from patients receiving Dicumarol therapy, show that alterations in prothrombin times are accompanied by corresponding alterations in coagulation times in silicone tubes, but not in glass tubes. The silicone coagulation time is not always changed on the same day as the prothrombin time, but changes are in the same direction consistently enough so that curves plotted to cover several days for both values have similar contours. There is no quantitative correlation which would make it possible to predict from an isolated prothrombin time what would be the silicone coagu-

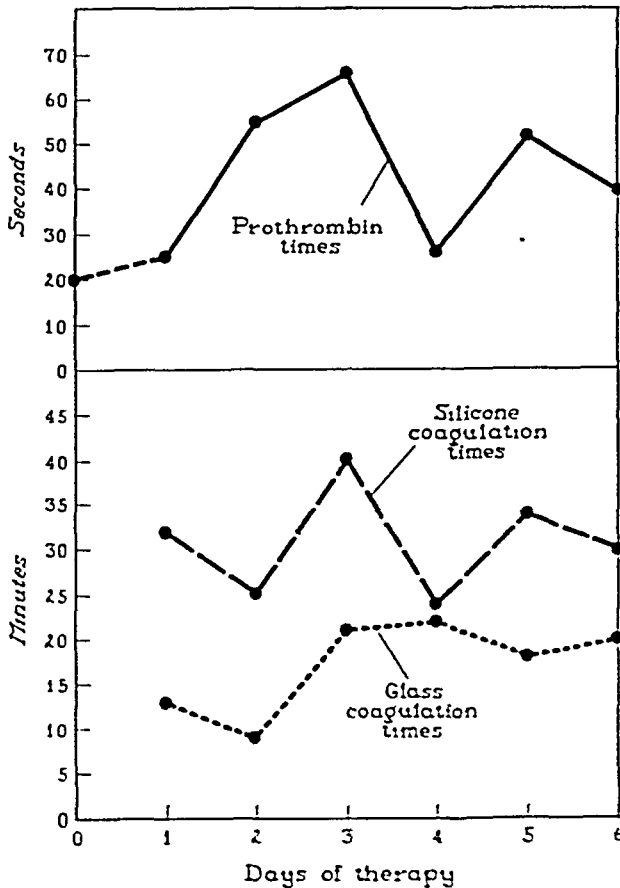


FIG. 3.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Female patient, aged 45 years, receiving Dicumarol prophylactically beginning 3 days after cholecystectomy.

lation time, as this varies greatly from one individual to the next.

The most immediate observation is that the silicone coagulation time represents a more sensitive measuring device than coagulation times done in glass. In most of the studies there was a change in silicone coagulation time in the manner anticipated from the change in prothrombin time. This was not correspondingly reflected in the glass tube.

In the same patients, however, results suggest that prothrombin time alone may not be the only altered part of the coagulation mechanism which is produced by administration of Dicumarol. This is apparent from the fact that

the same levels in 2 patients produce strikingly different coagulation times in silicone. This was especially marked in Patient 13, who resisted Dicumarol so long as judged by the prothrombin time, but in whom ultimately the prothrombin rose to the desired therapeutic level. The other factor (or factors) probably involves the rapidity of conversion from prothrombin to thrombin. One could explain these differences if one assumed that Tocantins' anticephalin substance<sup>6</sup> remained in the silicone-coated system, but was removed by the technic used in the prothrombin determination. This would delay the conversion of prothrombin to thrombin, giving a longer coagulation time.

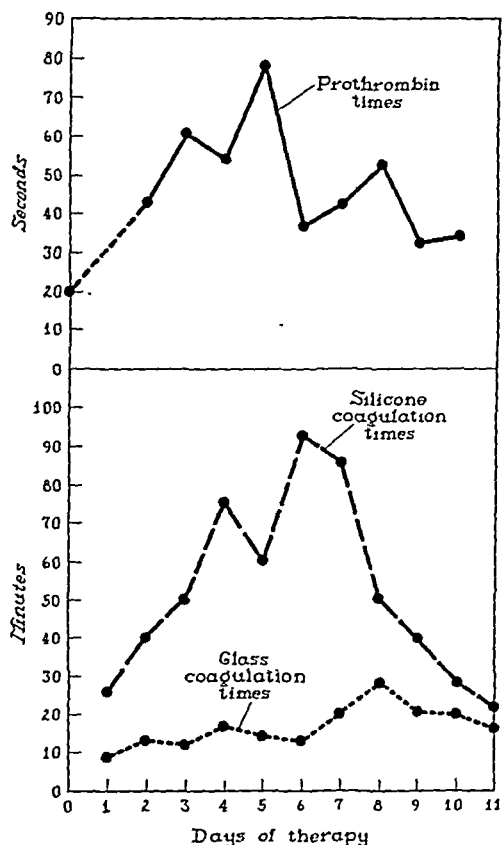


FIG. 4.—Relationship between prothrombin time, coagulation time in silicone tubes and coagulation time in glass. Male patient, aged 61 years, who had had acute thrombophlebitis after abdominoperineal resection. Administration of Dicumarol was begun immediately.

There may, contrariwise, be a substance which acts to hasten that conversion, giving an opposite action to that of the anticephalin. The occasional delay in the effect of Dicumarol on the coagulation time in silicone tubes as compared with its effect on the prothrombin time might then be due to the persistence of such an unknown factor, which eventually is exhausted or depressed by Dicumarol. Wright found evidence to indicate that platelets are more adhesive in the presence of glass, thus hastening coagulation, and Spooner and Meyer attributed at least some of the effect of Dicumarol to a lessening of this adhesiveness. The occasional rare individual who may form a thrombus despite a prothrombin time of 35 seconds would be one who converts even the smaller quantity of prothrombin in such a rapid manner as to produce a clot.

Since this work was done Moloney, Murphy and Harrington have shown a similar correlation between coagulation times in silicone-coated containers and prothrombin blood levels reduced by the administration of Dicumarol.

**Summary.** 1. Thirteen patients receiving Dicumarol were studied. It was found that the changes in prothrombin time in these patients were associated with corresponding changes in the coagulation time in silicone tubes. Glass tubes used to measure coagulation time in the conventional way did not show these changes.

2. The change in silicone-tube coagulation times was often not simultaneous with the change in the prothrombin time. Possible reasons for this lag are discussed.

3. The relationship between prothrombin time and silicone coagulation time varied from one individual to another. The same prothrombin time in several subjects was accompanied by widely different coagulation times, so that it was not possible to correlate directly the prothrombin time of the patients studied with the silicone coagulation time that they manifested. Change in prothrombin time was, however, accompanied by alteration in coagulation time which was consistently predictable in direction if not in magnitude.

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# A HEMATOLOGIC AND ELECTROPHORETIC STUDY ON BLOOD REGENERATION IN DOGS SUBJECTED TO REPEATED PHLEBOTOMY

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STUDIES by McKibbin and coworkers<sup>9</sup> have shown that dogs receiving a highly purified ration supplemented only with synthetic vitamins are able to regenerate hemoglobin rapidly following an extended series of bleedings. Dogs rendered anemic and hypoproteinemic by dietary means and hemorrhage invariably regenerate hemoglobin more rapidly than plasma protein on a variety of dietary regimens.<sup>12,15</sup>

The present investigation was undertaken to determine the ability of dogs with different dietary backgrounds to regenerate blood components when bled repeatedly over a period of several months.

**Materials and Methods.** Three dogs were used in these experiments. One had been maintained on a purified diet, No. 620†<sup>13</sup> supplemented with vitamins and 5% dried beef liver for 2 years. Another had received the same purified diet and vitamins without the liver supplement for the same period of time. Hematologic studies, conducted on these 2 dogs since they were given the experimental diets at weaning, revealed no abnormalities. They had, however, shown an impairment in ability to excrete bromsulfalein. The third dog was selected from our stock colony and had been fed a mixed diet consisting of Gaines' dog meal, fresh horse meat and milk. During the course of bleeding

the 3 dogs were continued on the same diets *ad lib*. The average daily food consumption was about 200 gm. In addition, daily iron supplements in the form of ferrous sulfate, were given: 20 mg. for the first month, followed by 50 mg. for the remainder of the test period. The total amount of iron, including that in the diet, which each dog received, was approximately 1.4 gm.

Each dog was bled by jugular vein puncture a total of 33 times (100 to 200 cc. taken about 3 times weekly) over a period of 2½ months. The volume of blood removed from each animal during this period totaled approximately 4850 cc. or about 5 times the original blood volume. This quantity of blood had a hemoglobin content of about 372 gm., equivalent to 1.24 gm. of iron.

At each bleeding, determinations were made of erythrocytes, hemoglobin, hematocrit, total and differential leukocytes, plasma fibrinogen, serum protein and albumin-globulin ratios. Estimations of reticulocyte and platelet numbers, prothrombin times, icteric indices and electro-phoretic components of plasma were made less frequently. Hemoglobin was determined colorimetrically in an Evelyn colorimeter. The quantity of hemoglobin regenerated was calculated from the difference in total hemoglobin in each animal between blood withdrawals. The total circulating blood volume was assumed to be 8% of the body weight.<sup>9,10</sup>

Prior to electrophoretic analysis the plasma samples were diluted 3 fold with barbiturate buffer and dialyzed at low temperature for periods ranging from 2 to 6 days in Visking

† Diet 620: Casein "Vitamin free" Labco, 30.0; Dextrose, 41.0; Crisco, 21.0; Corn oil, 0.15; Salt Mixture No. 1 U.S.P. XI, 3.0; Bone Ash, 2.85; Cod liver oil, 2.0. Daily Vitamin Supplement—oral: Thiamine, 1 mg.; Riboflavin, 1 mg.; Pyridoxine, 1 mg.; Nicotinic acid, 20 mg.; Calcium pantothenate, 40 mg.; Choline chloride, 200 mg.; Inositol, 200 mg.; Alpha tocopherol, 25 mg. weekly.

TABLE 1.—HEMATOLOGICAL AND BIOCHEMICAL CHANGES IN DOGS BLED REPEATEDLY.

| Dog No. | Diet  | No. of bleedings | RBC  | Hb   | Hcrit | MCV  | MCH  | WBC    | Total gm. Hb removed | Total gm. Hb regenerated | % Hb regenerated | Plasma protein gm. % | Fibrinogen mg./100 cc. | Wt.  |
|---------|-------|------------------|------|------|-------|------|------|--------|----------------------|--------------------------|------------------|----------------------|------------------------|------|
| 203     | 620   | 0                | 6.11 | 13.0 | 50.0  | 81.6 | 21.2 | 9,980  | —                    | —                        | —                | 6.4                  | 290                    | 14.0 |
|         |       | 12               | 4.71 | 9.4  | 41.0  | 87.0 | 19.9 | 11,840 | 155.0                | 103                      | 66.5             | 6.0                  | 330                    | 13.8 |
|         |       | 24               | 4.02 | 5.0  | 25.0  | 62.2 | 12.4 | 11,280 | 287.9                | 199                      | 69.3             | 6.2                  | 330                    | 12.4 |
|         |       | 29               | 3.25 | 4.8  | 22.0  | 67.8 | 14.8 | 12,880 | 336.5                | 236                      | 61.2             | —                    | —                      | 11.5 |
|         |       | 33               | 3.11 | 4.6  | 19.5  | 62.7 | 14.8 | 14,320 | 369.9                | 273                      | 73.8             | 6.1                  | 395                    | 11.1 |
| 204     | 620   | 0                | 6.50 | 13.6 | 49.0  | 75.3 | 20.9 | 11,520 | —                    | —                        | —                | 6.3                  | 200                    | 11.5 |
|         | plus  | 12               | 4.5  | 8.6  | 32.0  | 71.0 | 19.1 | 7,920  | 155.9                | 109                      | 69.9             | 5.9                  | 350                    | 11.4 |
|         | liver | 24               | 4.07 | 5.9  | 29.0  | 71.3 | 14.5 | 6,360  | 279.9                | 202                      | 72.1             | 6.6                  | 540                    | 10.5 |
|         |       | 29               | 3.77 | 5.7  | 24.0  | 63.6 | 15.2 | 6,400  | 333.0                | 233                      | 69.9             | —                    | —                      | 10.3 |
|         |       | 33               | 2.94 | 5.0  | 17.0  | 58.0 | 17.0 | 13,520 | 365.2                | 288                      | 70.6             | 6.2                  | 445                    | 10.0 |
| 587     | Stock | 0                | 6.89 | 14.5 | 50.0  | 72.6 | 21.1 | 12,920 | —                    | —                        | —                | 5.7                  | 210                    | 11.2 |
|         |       | 12               | 4.67 | 9.1  | 37.5  | 80.0 | 19.5 | 14,480 | 156.0                | 76                       | 48.7             | 4.7                  | 240                    | 11.3 |
|         |       | 24               | 4.3  | 6.3  | 29.0  | 67.5 | 14.7 | 13,240 | 285.7                | 182                      | 63.7             | 4.7                  | 210                    | 11.1 |
|         |       | 29               | 3.66 | 6.5  | 27.5  | 75.2 | 17.8 | 12,680 | 347.0                | 230                      | 66.3             | —                    | —                      | 10.9 |
|         |       | 33               | 3.41 | 5.2  | 20.0  | 59.0 | 15.2 | 10,640 | 384.0                | 256                      | 66.7             | 4.5                  | 230                    | 10.6 |

tubing against 2000 ml. of the same buffer mixture. The electrophoresis experiments were carried out by means of the Tiselius apparatus<sup>14</sup> in an analytical cell of the Tiselius-Longworth type<sup>8</sup> of 11.0 ml. capacity at 1.1°C., for a period of 240 minutes. The buffer consisted of 0.1 N sodium diethylbarbiturate and 0.02 N diethylbarbituric acid, pH 8.6, as recommended by Longworth.<sup>8</sup> The Schlieren scanning method of Longworth<sup>7</sup> was used to record the refractive index gradients in the cell. The percentage composition of the electrophoretically separable components was calculated from planimetric measurements of the descending boundaries, following enlargement of the records by projection and appropriate extrapolation. The patterns are, as a rule, rather complex and not completely resolved.<sup>1,2,16</sup>

**Results.** Table 1 shows some of the pertinent hematological and biochemical data obtained. All dogs showed a loss of body weight. The frequent bleeding of the animals was sufficiently severe to produce a progressive decrease in hemoglobin, erythrocyte, and hematocrit values. Nevertheless about 70% of the hemoglobin removed at each interval was regenerated. There appeared to be no significant difference in the ability of the dogs on the different dietary regimens to make up hemoglobin lost through hemorrhage. The data show the development in all 3 animals of a microcytic, hypochromic anemia. Dog 204, which received the purified diet supplemented with dried liver, suffered a decrease in leukocyte count within 2 weeks. This low count persisted throughout most of the experimental period but returned to normal after the 30th bleeding. All animals showed a slight relative decrease in

lymphocytes and a corresponding increase in neutrophils during the last month of treatment. No differences between animals occurred in reticulocyte and platelet counts, in prothrombin times or in icteric indices.

Occasionally during the course of the experiment the blood was noted to clot more rapidly than usual. This irregular finding could not be correlated with prothrombin values or platelet counts determined at the same intervals.

Two dogs were able to regenerate quite readily the plasma protein which was removed. The third animal, given the stock diet, suffered a decrease in this blood component early in the experiment from which it did not recover (Table 1). Plasma fibrinogen levels gradually increased in both animals maintained on purified diets. Since these animals had also shown at the onset of test an inability to excrete bromsulfalein rapidly, the elevated fibrinogen values suggested the existence of hepatic damage. Examination of histological sections of liver revealed the validity of this contention in one of the dogs. The liver of this animal, No. 203, showed centrilobular atrophy, necrosis and fatty degeneration. Biliary stasis was also evident in the central areas of the lobules. Large masses of iron-positive pigment were present throughout the liver. The spleen of this animal also contained considerable iron. The second dog (No. 204) fed the purified diet, likewise had stainable iron in liver and spleen.

The rapidity with which hemodilu-

TABLE 2.—HEMODILUTION AND REGENERATION AFTER WITHDRAWAL OF 200 CC. OF BLOOD.

|            | Dog No. | Time Interval |         |       |        |         |         |
|------------|---------|---------------|---------|-------|--------|---------|---------|
|            |         | 0             | 15 min. | 1 hr. | 6 hrs. | 24 hrs. | 48 hrs. |
| Serum      | 203     | 6.0           | 5.6     | 5.15  | 5.35   | 5.7     | 6.1     |
| protein    | 204     | 6.5           | 5.75    | 5.7   | 5.3    | 5.7     | 6.2     |
| gm. %      | 587     | 4.6           | 4.15    | 3.9   | —      | 4.25    | 4.5     |
| Hematocrit | 203     | 22.0          | 21.2    | 21.0  | 19.0   | 14.0    | 19.5    |
| vol. %     | 204     | 21.0          | 20.0    | 19.5  | 17.0   | 16.5    | 18.0    |
|            | 587     | 22.0          | 22.0    | 20.0  | —      | 17.0    | 20.0    |

tion occurred following removal of blood was studied immediately after the 32nd bleeding (200 cc.). Table 2 shows that in all three dogs both serum protein levels and hematocrits decreased within 15 minutes to 1 hour after phlebotomy. The serum protein levels were increasing by the 24th hour and were essentially normal by the 48th hour. On the other hand, the hematocrit values were lowest at the 24th hour and had not yet attained the base line values at the 48th hour. These data indicate that hemodilution occurs rather rapidly after withdrawal of blood and that the serum protein tends to be replaced at a more rapid rate than the erythrocytes.

Electrophoretic patterns obtained in these dogs initially and finally after 32 bleedings are shown in Figure 1. The plasma protein spectrum as determined by electrophoretic analyses is recorded in Table 3. At the onset of the test the dog getting stock diet had a higher proportion of albumin and a lower proportion of globulin than the dogs receiving purified diet. The lower proportion of globulin was due primarily to the beta-2 and gamma components. During the course of bleeding, the dog on purified diet without liver showed an increase in albumin and a decrease in total globulin whereas the other 2 animals showed the reverse effect. An increase in alpha-3 globulin and in

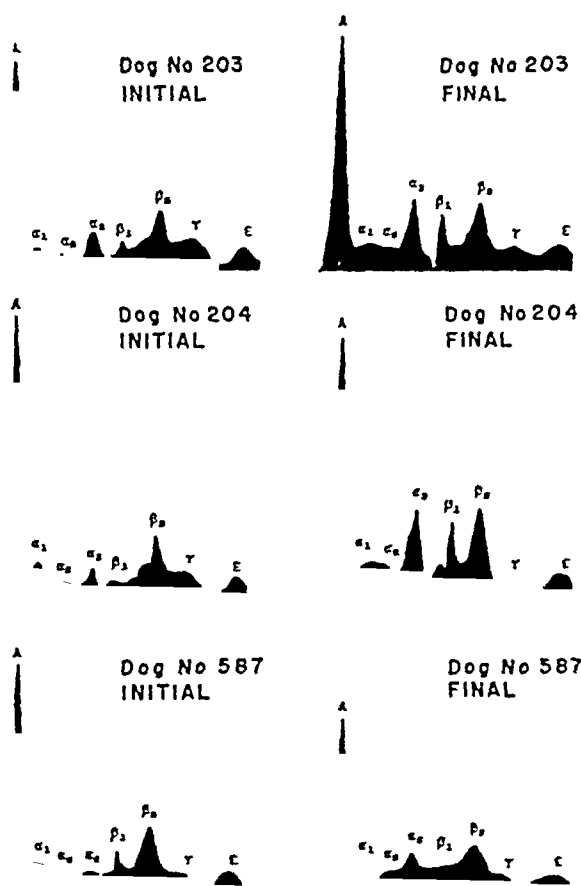


FIGURE 1.—Electrophoretic patterns of dogs obtained before and after 32 bleedings. The diets fed to the dogs were: Dog 203—Diet 620; Dog 204—Diet 620 plus liver; Dog 587—Stock diet. Note the increase in albumin (A) in dog 203 and decrease in this fraction in dogs 204 and 587. In general the dogs show a relative decrease in gamma globulin and increases in the beta-1 and alpha-3 globulin fractions of the plasma.

TABLE 3.—ELECTROPHORETIC ANALYSES OF PLASMA PROTEIN OF DOGS SUBJECTED TO REPEATED PHLEBOTOMY.

| Dog No. | Diet        | No. of bleedings | Albumin | Total Globulin | Globulin Fractions |            |           |           |          | A/G Ratio |
|---------|-------------|------------------|---------|----------------|--------------------|------------|-----------|-----------|----------|-----------|
|         |             |                  |         |                | $\alpha 1+2$       | $\alpha 3$ | $\beta 1$ | $\beta 2$ | $\gamma$ |           |
| 203     | 620         | 0                | 37.7    | 62.3           | 12.5               | 9.6        | 5.7       | 20.7      | 13.8     | 0.61      |
|         |             | 24               | 44.7    | 55.3           | 15.2               | 7.3        | 10.8      | 12.0      | 10.1     | 0.81      |
|         |             | 32               | 41.7    | 58.3           | 12.9               | 13.0       | 9.0       | 15.4      | 7.9      | 0.72      |
| 204     | 620 + liver | 0                | 41.9    | 58.1           | 15.0               | 6.2        | 7.7       | 17.7      | 11.5     | 0.72      |
|         |             | 24               | 39.1    | 60.9           | 15.6               | 14.3       | 8.7       | 17.0      | 5.4      | 0.64      |
|         |             | 32               | 37.0    | 63.0           | 13.3               | 14.6       | 11.2      | 17.1      | 6.9      | 0.59      |
| 587     | Stock       | 0                | 50.2    | 49.8           | 12.2               | 6.0        | 7.6       | 15.8      | 8.2      | 1.01      |
|         |             | 24               | 42.7    | 57.3           | 17.5               | 7.9        | 16.0      | 10.3      | 5.6      | 0.75      |
|         |             | 32               | 48.1    | 51.9           | 5.6                | 11.2       | 11.4      | 17.1      | 6.6      | 0.93      |

Total protein is taken as 100% and each protein component is indicated as a fraction thereof.

beta-1 globulin<sup>§</sup> occurred in all 3 dogs while the gamma globulin decreased. Following bleeding the dog on purified diet without liver showed a decrease of beta-2 globulin. The dog on stock diet showed an increase in alpha 1+2 globulin and later a decrease in these fractions. As a consequence of the foregoing changes in albumin and globulin the albumin-globulin ratio became larger in the dog on purified diet without liver but smaller in the other dogs.

A comparison was made of plasma albumin-globulin ratios determined on 6 samples of dog blood by: (a) electrophoresis, (b) Howe's salt fractionation method<sup>5</sup> and (c) the methanol method of Pillemer and Hutchinson.<sup>11</sup> The lat-

ter two methods gave results consistently higher than the first method (Table 4). This is in contrast to Pillemer's finding that in *human* serum there is better agreement between the results of electrophoretic analysis and his alcohol method of fractionation than between either of these two techniques and the salting-out method of Howe. However, we think that this point deserves fuller study in dogs before definite conclusions can be drawn.

**Discussion.** No striking differences were observed in the ability of dogs receiving different diets to regenerate hemoglobin following a series of rather severe bleedings. The lack of folic acid, p-aminobenzoic acid and biotin in the diet of one dog had no influence on

TABLE 4.—COMPARISON OF ALBUMIN-GLOBULIN RATIOS IN DOG PLASMAS AS DETERMINED BY DIFFERENT METHODS.

| Dog. No. | Bleeding No. | Electrophoresis | Albumin-Globulin Ratio                 |                     |
|----------|--------------|-----------------|--|---------------------|
|          |              |                 | Na <sub>2</sub> SO <sub>4</sub> (Howe) | Methanol (Pillemer) |
| 203      | 1            | 0.61            | 1.0                                    | 1.1                 |
|          | 24           | 0.81            | 1.5                                    | 1.95                |
| 204      | 1            | 0.72            | 1.7                                    | 1.5                 |
| 587      | 24           | 0.75            | 1.5                                    | —                   |
|          | 32           | 0.93            | 1.25                                   | 1.6                 |

§ The designation of the various protein components observed in dog plasma is not uniform in all laboratories. The reason for this divergence must be sought in varying degrees of resolution of the dog plasma pattern by different investigators and also in the fact that other authors have labeled as "fibrinogen" the component designated as Beta<sub>2</sub>-globulin in this paper, although it is evident that only a *fraction* of this electrophoretic component can actually consist of fibrinogen<sup>16</sup>. This component should perhaps be designated [Beta<sub>2</sub>+ $\rho$ ] rather than simply Beta<sub>2</sub> or  $\rho$ . If due allowance is made for the difference in terminology, the present data appear to be essentially in agreement with those reported by Zeldis *et al.*<sup>17</sup>

blood regenerating capacity. Michaud and associates<sup>10</sup> have shown that dogs on a purified diet, without folic acid or biotin (and even with succinylsulfathiazole added) are capable of adequate hemoglobin regeneration after profound exsanguination.

Two of the 3 dogs quickly replaced the total plasma protein removed. The third animal, while inefficient in this respect, nevertheless had, after the series of bleedings, about 70% of its original plasma protein level. On the other hand, the final hemoglobin levels of the dogs after bleeding were only about 35% of the original values. Thus plasma protein regeneration apparently took precedence over hemoglobin regeneration. This is in contrast to the condition which prevails in anemic, hypoproteinemic dogs in which hemoglobin is regenerated in preference to plasma protein.<sup>12,15</sup> Whipple, Robscheit-Robbins and associates,<sup>12,15</sup> however, provided more iron in the diet of their dogs than was given in the current experiments. Our dogs each received about 1.4 gm. of iron during the experimental period in which an average of 1.24 gm. was removed as hemoglobin. Iron intake, therefore, may have been the prime factor limiting hemoglobin production. However, since only about 0.9 gm. of iron could be accounted for in the regenerated hemoglobin and since stainable iron was observed in the livers and kidneys of 2 dogs, there remains the possibility that faulty utilization of iron contributed to the development of the microcytic hypochromic anemia.<sup>4</sup>

Although total plasma protein concentrations were regained completely or almost so in the dogs between bleedings, the relative concentration of their individual electrophoretic components showed alterations. Zeldis and Alling<sup>16</sup> have observed that after a single acute depletion of plasma protein by plasmaphoresis in dogs the electrophoretic

pattern may be disturbed for as long as 2 to 3 weeks after the initial total protein level has returned to normal. In dogs so depleted plasma globulin restoration proceeds more rapidly than plasma albumin restoration. An increase in beta globulin and fibrinogen has been observed in dogs also with severe vascular disease<sup>6</sup> or hepatitis and cholangitis.<sup>16</sup>

Our data, showing that albumin-globulin ratios are lower when determined by electrophoresis than by Howe's method, agree with those of Chow and associates<sup>1</sup> in dogs and Dole and Braun<sup>3</sup> and Deutsch and Goodloe<sup>2</sup> in humans. Chow believes this finding is due to incomplete separation of the globulins from albumin by the method of Howe.

The 3 dogs used in these experiments exhibited a slight but continued weight loss as a consequence of repeated exsanguination. This indicates that the protein stores of the body were drawn upon for regeneration of blood components so incessantly that their replacement by synthesis from ingested food became inadequate.

**Summary.** Repeated phlebotomy in adult dogs, maintained on diets containing 25 to 30% protein resulted in the development of a microcytic, hypochromic anemia. No differences, ascribable to the dietary regimen, were observed in the ability of the dogs to synthesize hemoglobin.

After a single withdrawal of blood, hemodilution occurred within one hour. Serum protein levels were essentially normal 48 hours later, but hematocrit values were still depressed.

Throughout the course of bleeding, plasma protein production took precedence over hemoglobin production. The possibility exists that this condition may have been due, in part, to iron lack or faulty iron utilization.

As a result of bleeding, an increase in total globulin and a decrease in

albumin was observed in a dog on a purified diet supplemented with liver and in another fed a natural stock ration. The reverse effect occurred in a dog given a purified diet without liver.

Electrophoretic studies revealed a

relative decrease in gamma globulin and increases in the beta-1 and alpha-3 globulin fractions of the plasma in all 3 dogs following repeated removal of whole blood.

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**Observations.** 1. ILLUSTRATIONS OF ANTICOAGULANTS AFFECTING SERIAL DILUTIONS OF WHOLE PLASMA PROTHROMBIN. Fig. 1 represents arbitrary dilutions of normal plasma, plasma obtained from a heparinized normal individual, plasma obtained from a dicumarolized normal individual, and plasma obtained from an untreated patient with pulmonary infarction which contained an anticoagulant-like substance (auto-anticoagulant). These dilutions were

curve it is evident that heparin exerts a maximum effect upon the whole plasma prothrombin time and a slight effect upon the more dilute prothrombin times when compared with the curve of normal plasma. The effect upon the prothrombin time of heparin is immediate and is usually not detectable 4 hours after it is administered parenterally. The action of heparin is also observed in a prolongation of the coagulation time.

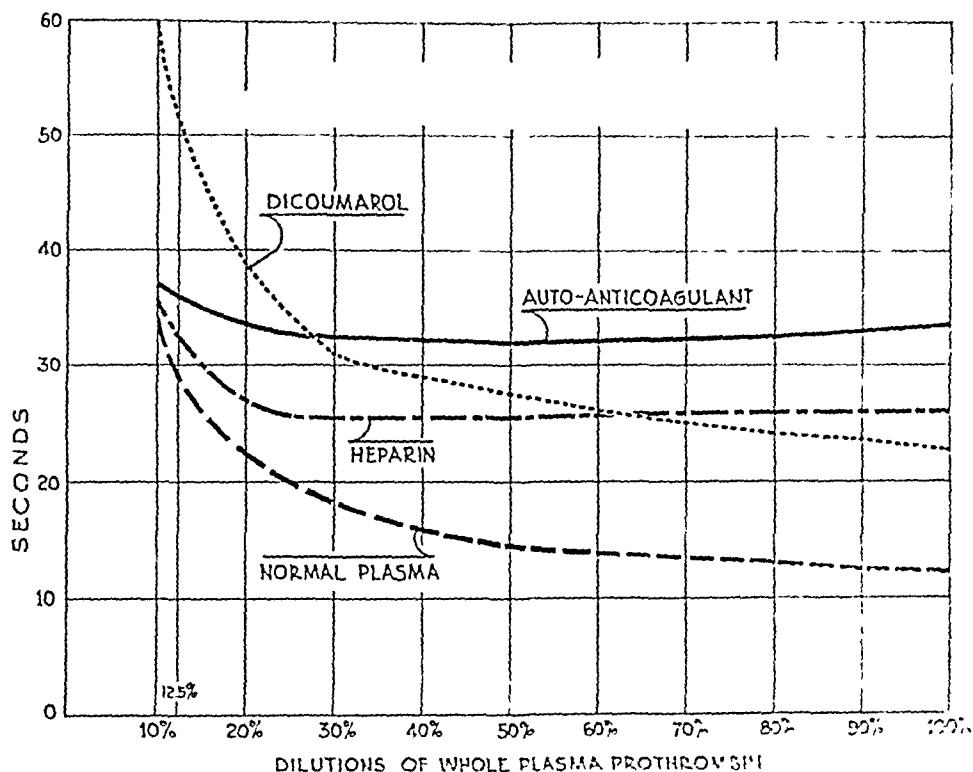


FIG. 1.—Effect of auto-anticoagulant, Dicumarol and heparin on whole and dilute plasma prothrombin.

made by diluting whole plasma with physiological saline solution according to the method outlined by Quick.<sup>9</sup>

The dilution curve of whole plasma prothrombin shown here is a representative one for rabbit lung thromboplastin. The heparinized plasma dilution curve illustrated is from a normal individual whose blood was taken 45 minutes after administration of 50 mg. of heparin intravenously. From this

The dicumarolized plasma represented in Fig. 1 is from a normal individual on daily therapeutic doses (50 to 150 mg.) of Dicumarol. Prolongations in prothrombin times of dicumarolized plasma occur in all dilutions as illustrated in this figure. Dicumarol produces a moderate prolongation of the whole plasma prothrombin time and a marked prolongation of the dilute plasma prothrombin time.



2. METHOD OF DETERMINING HEPARIN AND DICUMAROL DOSAGE DURING THE INITIAL PHASE OF COMBINED ANTICOAGULANT THERAPY. After an initial therapeutic dose of Dicumarol (300 mg.) there is an average lag phase of 48 hours before its hypoprothrombinemic effect is obtained. Inasmuch as heparin administered parenterally has an instantaneous effect upon coagulation and whole plasma prothrombin times, therapeutic amounts of heparin and Dicumarol are given simultaneously to obtain an immediate anticoagulant effect. We have found that the 12.5% plasma prothrombin time is the best guide to Dicumarol therapy during the first 48 hours. This is because the 12.5% plasma prothrombin time is only slightly affected by heparin as illustrated in Fig. 1. If Dicumarol is given according to the prolongation of the whole plasma prothrombin time during this period, insufficient dosage will be administered since the prolongation of the whole plasma prothrombin time may be due to the effect of heparin. The obvious method is to take the blood for prothrombin determination at least 4 hours after parenteral heparin administration. However, whether heparin is administered continuously by intravenous drip or in Pitkin's menstruum or intermittently during the lag phase of dicumarol, the prolongation of the 12.5% plasma prothrombin time is the most accurate guide to the hypoprothrombinemic effect to Dicumarol. From our experiences during the combined use of heparin and Dicumarol we have concluded that the whole plasma prothrombin time should be done routinely. However, during this period the 12.5% dilute plasma prothrombin time is the significant determination upon which Dicumarol dosage is based.

3. DISEASES IN WHICH ANTICOAGULANT-LIKE SUBSTANCE (AUTO-ANTICOAGULANT) HAS BEEN OBSERVED. The effect of the anticoagulant-like substance

present in the diseases to be enumerated is detected in the whole plasma prothrombin time but is usually undetectable in the 12.5% plasma since the substance is generally rendered ineffective by diluting 1:8.<sup>11</sup> This effect upon the whole plasma prothrombin time with little or no change in the dilute plasma prothrombin time has been observed in diseases associated with thrombosis, inflammation or necrosis, as shown in Table 1.

TABLE 1.—DISEASES ASSOCIATED WITH ANTICOAGULANT-LIKE SUBSTANCE

| Diseases                                       | Number of cases |
|--|-----------------|
| Myocardial Infarction . . . . .                | 70              |
| Phlebothrombosis or Thrombophlebitis . . . . . | 45              |
| Pulmonary Infarction . . . . .                 | 23              |
| Acute Cholecystitis . . . . .                  | 4               |
| Carcinomatosis . . . . .                       | 12              |
| Acute Rheumatoid Arthritis . . . . .           | 2               |
| Acute Rheumatic Fever . . . . .                | 4               |
| Fractures . . . . .                            | 9               |
| Cerebro-Vascular Accidents . . . . .           | 7               |
| Arterial Emboli and Thrombosis . . . . .       | 6               |

The nature of this anticoagulant-like substance is apparently an inhibiting agent not concerned with the production of prothrombin. The 12.5% plasma prothrombin time can be normal when the whole plasma prothrombin activity is as low as 10%. A normal 12.5% plasma prothrombin time indicates a normal amount of prothrombin present. To cite an example of the extreme quantitative effect of anticoagulant-like (auto-anticoagulant) substance, we recently observed a case of superficial thrombophlebitis of the right leg following trauma to that leg. The patient was a 67 year old female with moderate bilateral saphenous varicosities. She was admitted 2 days following a pulmonary embolus. At this time the patient had a coagulation time of 40 minutes, a whole plasma prothrombin time of 33.5 seconds (normal, 12.5 seconds), and a 12.5% dilute plasma prothrombin time

of 35.7 seconds (normal, 28.5 seconds). On admission the patient was acutely ill and was treated solely with Dicumarol and supportive therapy as only a slight degree of prothrombin deficiency was present. Twenty-four hours later the coagulation time was normal and the inhibitor effect in the prothrombin times was less marked than it was upon admission. At this time heparin was also given until the dilute plasma prothrombin time showed a prolongation to a therapeutic Dicumarol range.

The impressions cited here have been observed during the performance of approximately 9,000 serial prothrombin determinations on a control series of patients.

A dilution curve of plasma containing the anticoagulant-like substance (auto-anticoagulant) closely resembles that of heparinized plasma as illustrated in Fig. 1. Knowing that protamine sulfate possesses the ability to remove heparin from blood *in vivo* and *in vitro*, we have attempted to remove the anticoagulant-like substance (auto-anticoagulant) from the plasma with protamine (*in vivo* and *in vitro*). In no instance have we been able to eliminate the anticoagulant-like (auto-anticoagulant) effect by protamine sulfate. This leads us to believe the substance observed by us is not heparin. The effect of prolongation of the whole plasma prothrombin time caused by the anticoagulant-like substance has in each instance been observed to disappear following operation, if due to acute surgical inflammatory disease. Similarly, it disappears with subsidence of infection or resolution and fibrosis if from myocardial infarction.

Doles<sup>6</sup> reports the presence of hypoprothrombinemia in acute coronary thrombosis and has treated these patients with vitamin K. He believes the hypoprothrombinemia is an indication of hemorrhage. We too have

used vitamin K in the presence of the inhibiting agent but we have not observed any change in the prothrombin time. Indeed, it would have surprised us to obtain a change in the prothrombin determination in the presence of the inhibiting agent, inasmuch as the dilute prothrombin time is essentially normal in its presence and does not indicate a hypoprothrombinemia.

4. PRESENCE OF HYPERCOAGULABLE AND ANTICOAGULANT-LIKE SUBSTANCE IN MYOCARDIAL INFARCTION, PHLEBITIS AND PULMONARY EMBOLISM. In patients with coronary symptoms we have performed serial prothrombin determinations along with the routine work-up for this disease. Several have been observed during the coronary insufficiency stage before a definite myocardial infarction occurred. Most of the prothrombin determinations were normal in both the whole and 12.5% dilute plasmas during this stage. During the observation period 11 patients developed typical myocardial infarctions substantiated clinically and electrocardiographically. At the time of the occlusion these patients have a diminished whole or 12.5% dilute plasma prothrombin time or both (hypercoagulable). The hypercoagulable (accelerator) effect occurs concomitantly with the onset of myocardial infarction. We believe that the prothrombin determination is inadequate in predicting myocardial infarction. An illustration of what occurs to the prothrombin time in myocardial infarction may be seen in Fig. 2. The presence of the anticoagulant-like substance has been observed as early as the first day following myocardial infarction and has usually disappeared by the 3rd to 6th week depending upon the extent of the myocardial infarct as seen in Fig. 2.

The individual with a massive hypercoagulable (accelerator) effect may continue to illustrate this action in the 12.5% plasma during the anticoagulant-

like phase. For example, during the anticoagulant-like phase the 12.5% plasma prothrombin time may be: 1, shorter (accelerated); 2, normal; 3, slightly prolonged or inhibited. This indicates: 1, an increased tendency to clot; 2, a normal prothrombin content; 3, evidence of increased anticoagulant-like substance affecting even the 1:8 dilution.

In difficult diagnostic conditions such as phlebothrombosis and pulmonary infarction, the prothrombin determination of whole and 12.5% plasma is of definite diagnostic value. During the early thrombotic period the times of either whole plasma, dilute plasma, or both determinations will be shorter than normal (accelerator phase). This is followed shortly by a prolonged

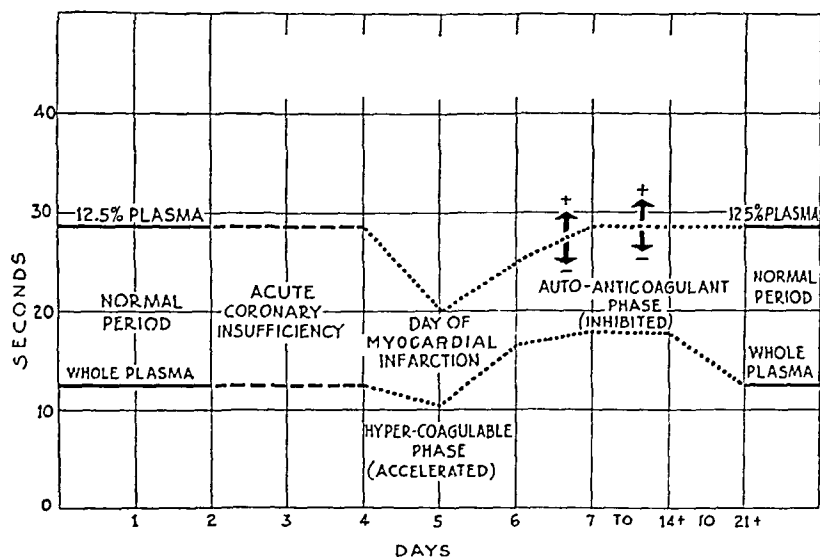


FIG. 2.—Whole and 12.5% dilute prothrombin times in myocardial infarction.

TABLE 2.—EXAMPLES OF PLASMA CONTAINING NATURALLY OCCURRING HYPERCOAGULABLE AND ANTICOAGULANT-LIKE SUBSTANCES

|   | Whole Plasma<br>Prothrombin<br>Time<br>(seconds) | 12.5% Plasma<br>Prothrombin<br>Time<br>(seconds) |
|---|--|--|
| 1. Normal Plasma  | 12.5   | 28.5   |
| 2. Hypercoagulable Plasma, Marked Effect                          | 10.0   | 20.0   |
| 3. Anticoagulant-like Plasma, Marked Effect                       | 18.0   | 34.0   |
| 4. Anticoagulant-like Plasma, Moderate Effect                     | 15.0   | 28.5   |
| 5. Anticoagulant-like Plasma, with Hypercoagulable Effect Present | 18.0   | 24.0   |

whole plasma prothrombin time (auto-anticoagulant phase). However, it must be emphasized that these changes may be influenced by certain inflammatory processes already existing.

Ware *et al.*<sup>12</sup> have demonstrated the presence of an Ac-globulin accelerator factor in normal plasma. With increasing concentration of the Ac-globulin accelerator factor the prothrombin time is made shorter. This plasma Ac-globulin is probably an inert protein or a pro-enzyme.<sup>13</sup> The isolation of this factor clarifies the mechanism of the conversion of prothrombin and fibrinogen to fibrin. Whether this factor is the one responsible for the hypercoagu-

lable plasmas which we have observed is unknown to us.

**Discussion.** Taking into consideration the presence of a naturally occurring anticoagulant in the above diseases outlined, the fact that thrombosis does not occur in some of these conditions poses the question: Is this Nature's way of preventing thrombosis? In follow-up cases of myocardial infarction, some plasmas have been found to be hypercoagulable. Many of these patients have typical anginal symptoms and others are symptom-free. The question is raised of whether to use prophylactic anticoagulant therapy (Dicumarol) in the presence of hypercoagulability preceding or following myocardial infarction. Hypercoagulable plasmas have been found pre-operatively as well as post-operatively. Some of these patients have a history of phlebitis and others of varicose veins. Whether patients with hypercoagulable plasmas are candidates for phlebothrombosis and pulmonary embolism is a question which needs

further investigation. A large series of cases demonstrating this phenomenon will have to be reviewed before a definite conclusion can be drawn.

**Summary.** 1. A review of the literature on naturally-occurring heparin-like substances is presented.

2. The action of heparin upon the prothrombin time is illustrated and compared with the effect of Dicumarol on the prothrombin mechanism.

3. From the whole and dilute prothrombin determinations there is devised a simple plan for adequate regulation of heparin and Dicumarol during the initial combined anticoagulant treatment of thromboembolic diseases.

4. The presence of naturally-occurring hypercoagulable (accelerator) and anticoagulant-like substances is illustrated with cases cited.

5. The prothrombin mechanism in relation to thromboembolic diseases, particularly myocardial infarction, is investigated and evaluated.

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## CONTINUOUS PERITONEAL IRRIGATION IN THE TREATMENT OF INTRACTABLE EDEMA OF CARDIAC ORIGIN\*

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THE treatment of edema, occurring in the course of chronic congestive heart failure, is in a more satisfactory state today than at any time in the past. By the sufficiently frequent administration of mercurial diuretic agents and, or, a sodium poor diet, together with other rational measures for the treatment of congestive heart failure (rest, digitalis, oxygen), in most instances water retention can be effectively combated. With the patient suffering from congestive heart failure properly trained on a salt poor regime, no longer are the stringent fluid limitations of former years in order. Recent work adequately establishes<sup>6,7</sup> the fact that such fluid limitation is not only unnecessary but distinctly detrimental.

Notwithstanding the general effectiveness of the regime outlined above, an occasional patient is encountered whose edema (or anasarca) responds little or not at all to the measures mentioned. In such patients recourse to other diuretic agents (ammonium chloride, potassium salts, urea, aminophyllin) has been of little value in our experience. Even in instances of established hypoproteinemia, when the strikingly lowered serum albumin seemed to play some part in the genesis of the intractable edema, all clinical measures available to us for the amelioration of the hypoproteinemia proved futile.

The patient in chronic congestive heart failure who responds to mercurial injection with satisfactory diuresis does so, it is believed, because the mercurial acts on the renal tubule, reducing sodium reabsorption. Thus there is a large increase, not only in the total sodium output, but also in the concentration of sodium in the urine.<sup>3</sup>

The patient in heart failure, with extensive water retention, who manifests little or no diuresis after the administration of mercurhydri or salyrgan, is one in whom such mercurial administration results in little or no additional sodium excretion. Marked reduction in glomerular plasma filtration leads quite obviously to parallel reduction in the amount of salt filtered through the glomerulus into the tubule. This means, as Leiter has indicated,<sup>5</sup> that, as effective as mercury may be in reducing tubular reabsorption (rarely below 96%), in such instance the amount of sodium filtered and failing of reabsorption (and hence excreted) may be insignificant.

Leiter<sup>5</sup> has taken advantage of the necessity of removing ascitic fluid in patients with intractable cardiac edema and ascites by carrying out peritoneal dialysis with the instillation of several liters of 5% glucose. The fluid is removed from the peritoneal cavity after 2 or 3 hours, and is found to contain almost as much salt as the plasma. This

\* The author wishes to acknowledge his indebtedness to Dr. S. L. Cohen, who cooperated in the medical management of this case, and to Dr. J. Birnbaum, who performed the necessary surgical measures.

procedure is reported to have the same effect on the individual as an effective dose of mercurial—a profuse diuresis.

We recently encountered a patient with chronic congestive heart failure whose edema was as massive as any we have seen. As detailed below, all the usual measures for securing diuresis proved futile. During 9 days of observation and treatment the fluid retention became progressively more marked. There was no ascites demonstrable on physical examination. Having in mind the technique described by various workers for continuous peritoneal irrigation,<sup>1,2,4,8</sup> we reasoned that considerable sodium loss from the body might be achieved in this case if a suitable fluid were used with such technique. It should be noted that in acute renal insufficiency the irrigating fluid is chemically designed, among other things, to maintain the prevailing state of fluid and electrolyte balance. The objective is solely to provide, in acute reversible renal insufficiency, an extra-renal mechanism for the excretion of nitrogenous and other waste products which, under ordinary circumstances, would be excreted by the kidneys. Our objective, on the other hand, was to use the same technique of continuous peritoneal dialysis, but only for the purpose of ridding the body of considerable sodium (and water). Five per cent glucose was used in this case.

To our knowledge, this is the first case report of a patient with intractable cardiac edema treated by the method of continuous peritoneal irrigation.

**Report of Case.** Mrs. F. W., 47 years of age, white, married, and nulliparous, was readmitted to the Jewish Memorial Hospital on August 7, 1948. She complained of shortness of breath and marked swelling of the abdomen and all four limbs. She had had several attacks of rheumatic fever in childhood, after which she invariably had dyspnea on mild effort. During the past 10 years this symptom became progressively more marked. Since September, 1947, she took digitalis consistently,

and received mercurhydrin injections once weekly. In February, 1948, 7 months before the present admission, she was admitted to the Jewish Memorial Hospital in a critical state with a diagnosis of rheumatic heart disease, mitral stenosis, auricular fibrillation and severe right and left congestive heart failure. Treated by rest in bed, digitalis, very frequent mercurial injections, oxygen, and fluids *ad lib.*, she improved dramatically, and on her discharge, April 1, 1948, after a hospital stay of 37 days, she weighed 67 pounds less than on admission. She was ambulatory at the time.

Following discharge from the hospital, the patient continued on oral digitoxin, 0.2 mg. daily, and received repeated injections of mercurhydrin. How carefully she followed a sodium poor diet is questionable. In spite of marked limitation of physical effort, she became progressively more dyspneic on effort, and finally, orthopneic. At the same time her lower extremities became more and more swollen, and in the several weeks before admission her abdomen and upper extremities likewise became swollen. When her orthopnea finally became intolerable the patient was readmitted to the hospital by ambulance.

The family history revealed only that the patient's mother, having suffered from heart disease for many years, died at the age of 50, either of heart failure or a "heart attack".

**Physical examination** on admission revealed a very seriously ill patient. Blood pressure 130/80. She was markedly cyanotic and orthopneic. There was auricular fibrillation and a heart rate of 90 per minute. Conjunctivae were suffused. Ocular fundi were normal, excepting for marked venous congestion. Facial edema was noticeable. Even in the full sitting position there was marked engorgement of the cervical veins. Coarse moist rales were audible throughout the chest. The heart was markedly enlarged, with the classical signs of mitral stenosis. Rate and rhythm as mentioned. The abdominal wall was so edematous, especially laterally and in the suprapubic region, as to be obviously several inches thicker than normal. The hepatic edge was palpable 3 fingers breadth below the costal margin, firm and not tender. No physical signs of ascites could be elicited. There was massive edema of both lower extremities from the feet through the groins. This edema of the lower extremities was more marked than in any case we can recollect. Both forearms were likewise very edematous, though not gigantically.

**Laboratory examination** revealed hemoglobin 11.2 gm., erythrocytes 5,400,000; leukocytes and differential count within normal

limits. Blood Wassermann test was negative. Repeated urine examinations revealed specific gravity always between 1010 and 1012. Albumin was consistently 3 plus, and at all times there were numerous hyaline and granular casts. Sedimentation rate within normal limits. Blood chemical examination revealed urea nitrogen varying between 32 and 59 mg. per 100 cc., and blood sugar, serum albumin, serum globulin, cholesterol within normal limits. Standard urea clearance was 17% of normal. Roentgen-ray (portable) examination of chest disclosed marked enlargement of the heart to the right and left, no infiltration or consolidation demonstrable in lung fields. Electrocardiogram disclosed marked right axis deviation and auricular fibrillation with ventricular rate of 90 per minute.

The *diagnosis*, as on the previous admission, was: rheumatic heart disease, mitral stenosis, auricular fibrillation and severe right and left congestive heart failure. In addition, there was renal damage and renal insufficiency with nitrogen retention.

*Treatment.* The measures which had proven so successful in the management of this patient on the first admission were to no avail. On several occasions mercurhydrin and salyrgan injections were without any effect on the patient's urine output, which remained consistently at 500 to 600 cc. per 24 hours. It was thought unwise to continue mercurial injections under these circumstances. On September 14 the patient was noted to be amaurotic. Neither we nor the ophthalmologic consultant could detect any pertinent fundus or other changes to account for the blindness.

With some misgivings it was finally decided, since the patient was growing worse with greater accumulation of edema, to institute continuous peritoneal irrigation, using 5% glucose with added penicillin. Accordingly, on September 16, 1948, 9 days after the patient's readmission, a No. 24 mushroom catheter and a sump drain were inserted into the peritoneal cavity, the former in the right subcostal region and the latter above the left groin. The connections and apparatus were essentially as described by Seligman, Frank, and Fine,<sup>8</sup> and others.<sup>1,2,4</sup> Penicillin in conventional dosage was administered intramuscularly throughout the period of irrigation. During the interval from September 16 to September 22, 500 to 1000 cc. of 5% glucose per hour were permitted to flow into the peritoneal space. Although improvement was visible, on September 22 the amount was curtailed to 200 cc. per hour because of the poor outflow, and on September 24 both the catheter and sump drain were removed because of scant return. At no time did the

patient manifest any symptoms of peritonitis.

On September 20 there was a striking improvement in the appearance of the patient. The facial edema had cleared entirely as had the edema of the forearms. The lower limbs were much less edematous. The edema of the lower extremities continued to diminish rapidly and on September 24, when the catheter and sump drain were removed, there was only minimal pretibial edema. Also on that day the patient was observed to have recovered her vision completely. We have unfortunately, no record of the weight change in this patient, since, when her edema was maximal, our nursing staff found the patient too immobile to get her out of bed for weighing. We are certain, however, that she lost more edema fluid between September 16 (the day the procedure was started) and September 24 (the day it was terminated) than during her previous hospital stay, and on that occasion she lost 67 pounds. The measurements in Table 1 will give some idea of the dramatic decrease in edema.

TABLE 1. COMPARATIVE CIRCUMFERENCES BEFORE AND AFTER PERITONEAL IRRIGATION

|          | L. calf | R. calf | At level of<br>Iliac crests |
|----------|---------|---------|-----------------------------|
| Sept. 15 | 60 cm.  | 58 cm.  | 121 cm.                     |
| Sept. 25 | 30 cm.  | 29 cm.  | 100 cm.                     |

Serum sodium determination on September 16, before the lavage was started, was 343 mg. per 100 cc. Daily determinations until September 24, the date of discontinuance, disclosed progressive fall in this level to 291 mg. per 100 cc. Total proteins remained unchanged. CO<sub>2</sub> combining power fell progressively from 48.5 to 37.6 vols.%. The drainage fluid at all times contained significant concentrations of sodium, varying from 312 mg. per 100 cc. to 331 mg. per 100 cc.

*Comment.* This case is reported for the sole purpose of recording the fact that continuous peritoneal irrigation with 5% glucose was followed by striking diminution of edema of cardiac origin in a patient in whom conventional measures had proved futile. Experience in one case of course does not justify a conclusion that this treatment is indicated in all cases of similar character; but it does suggest, we believe, that further study of extrarenal means of depleting body sodium is warranted. Nor are we convinced that

5% glucose is the best possible solution for this purpose. Conceivably a more physiologically acceptable solution can be designed. It is also suggested, if further experience proves the method to be clinically feasible, that it may be applied as well in certain selected cases of non-cardiac edema, if in those instances the continued accumulation of body water threatens the life of the patient. The decrease in body water by the measure described is in accord with the prevailing concept of the role of sodium in cardiac edema. Although no unfavorable results have been observed as a result of the surgical

procedure, it is obvious that it should not be employed except in severe cases where non-surgical treatment has been without avail.

**Summary.** 1. Continuous peritoneal irrigation with 5% glucose was used in a case of congestive heart failure with massive edema in whom conventional measures proved futile.

2. This procedure was followed by great loss of edema fluid and "short term" striking improvement of the patient.

3. The drainage fluid from the peritoneal cavity contained significant concentrations of sodium.

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# STUDIES OF A SULFADIAZINE-SULFAMERAZINE COMBINATION WITH SPECIAL REFERENCE TO TREATMENT OF PNEUMONIA\*

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CHEMICAL and therapeutic studies of sulfonamide combinations have demonstrated that the total amount of sulfonamide that can be held in solution in urine is substantially increased when two or more of these substances are administered simultaneously.<sup>1,2,5,6</sup> Thus it is possible to diminish the hazard of irritation to the urinary tract from sulfonamide crystals or calculi by means other than administration of alkali. Since sodium bicarbonate or other alkalizing adjuvants, to be completely effective in lowering the incidence of renal complications, must be given in amounts capable of causing undesirable effects, there is reason to believe that the use of sulfonamides in mixtures is advantageous.

The opinion has been prevalent, particularly among laboratory investigators, that combinations of sulfonamides in mixtures offered no advantage from the purely chemotherapeutic standpoint over the single compounds. Some held that mixtures would be less ef-

fective. However, clinical experience, especially that of Lehr,<sup>5,6</sup> suggested that combined sulfonamides were more efficacious. Zeller, Hirsh, Sweet, and Dowling<sup>9</sup> compared the response to sulfadiazine and sulfamerazine, administered simultaneously, to that obtained when the single drug was used in the treatment of meningococcic meningitis. There was a slight, but not significant, difference in case fatality rates with combined drug therapy, but no difference in the clinical course. Toxic reactions occurred with somewhat greater frequency, possibly as a result of the higher daily dosages of the sulfonamides used in combination. Differences observed were minimal and of uncertain significance.

During the past 3 years, sulfonamide mixtures† have been used at this hospital in treatment of pneumonias and other acute systemic infections††. In this paper, the results in treatment of pneumonia have been compared with those obtained by use of sulfadiazine

\* This work was aided by a grant from the Research Fund for Infectious Diseases, University of Pennsylvania, Philadelphia, Pennsylvania.

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† Sulfadiazine-sulfamerazine mixtures used in our studies were supplied as Combisul-DM by Dr. Norman L. Hemmway, Schering Corporation, Bloomfield, New Jersey.

†† Clinical facilities were given us for this study by the following Chiefs of Service: Doctors Frieda Baumann, R. S. Boles, C. L. Brown, Thomas Durant, Thomas Klein, D. W. Kramer, D. N. Kremer, W. G. Leaman, Jr., S. A. Loewenberg, and T. G. Schnabel.

alone, from the standpoint of chemotherapeutic effectiveness, toxic manifestations, and the occurrence of crystals of sulfonamide in urine. The latter may be presumed to represent, for the purpose of this comparison, the hazard of mechanical injury to the urinary tract related to low solubility of the sulfonamides used and their derivatives.

**Experimental.** Two separate therapeutic experiments were conducted. The first employed as subjects the patients with a diagno-

carbonate daily. Patients receiving sulfadiazine or sulfamerazine also received sodium bicarbonate in this amount. Except for the subgroup of 28, none of the patients receiving the drug mixture received alkali adjuvants.

If the patient failed to show evidence of a satisfactory clinical response to sulfonamide medication within 24 to 48 hours after starting therapy, an antibiotic was prescribed as a supplement. Patients who were desperately ill on admission received combined sulfonamide and penicillin therapy and neither these nor the preceding were included in the evaluation of therapeutic response. However, urine specimens from these patients were examined

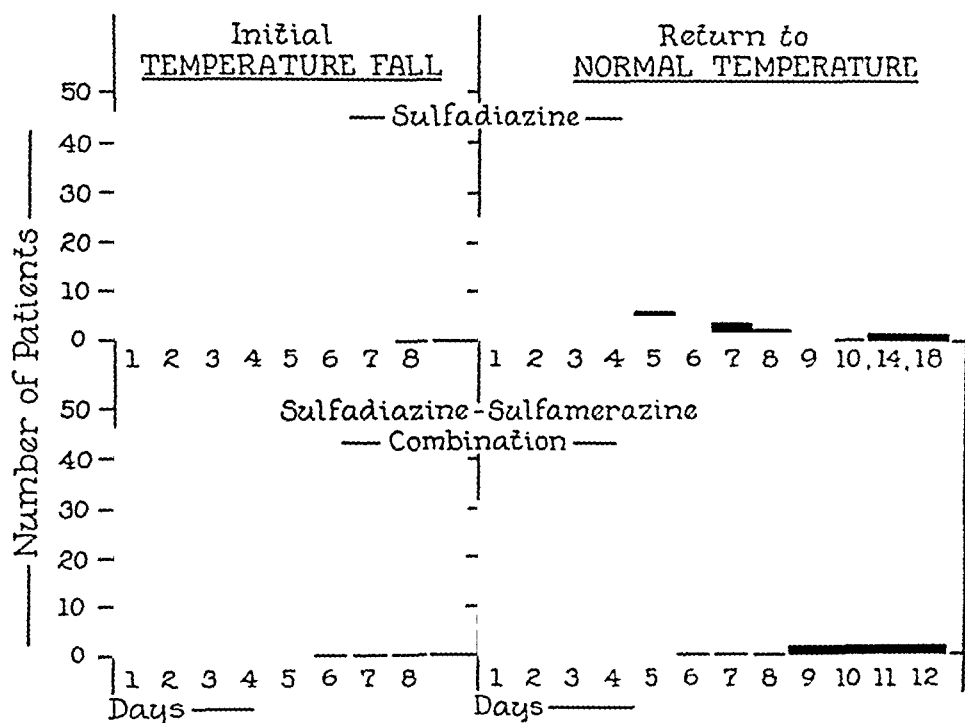


Fig. 1.—The response of patients treated with a sulfadiazine-sulfamerazine combination compared with that to sulfadiazine alone.

sis of pneumonia on the Fever Ward of the hospital from February to June, 1946. Since this included only a portion of the pneumonia season, a second series was investigated, starting in December, 1946, and continuing through May, 1947. The plan was that used in previous therapeutic trials by our group, assigning the patients systematically, without selection, to the several treatments that were under comparison. One hundred and sixty-nine patients received a mixture of equal parts of sulfadiazine and sulfamerazine, while 139 received sulfadiazine alone, and 45 sulfamerazine alone. An additional group of 28 patients received the sulfonamide mixture, but, in addition, were given 6 gm. of sodium bi-

regularly for presence of sulfonamide crystals.

The problems arising in connection with the diagnosis of pneumonia have been discussed in a recent paper from this hospital<sup>4</sup> and the reader is referred to it for information concerning the patients undergoing study, as well as the factors influencing the diagnosis. In previous reports, a statement was made that the diagnosis of typical pneumonia was established in every case by the natural history of the disease, the findings on physical examination, and, when indicated, by roentgenological studies. As a result of knowledge gained in recent years, it must now be recognized that by these criteria and by the findings on sputum cultures it is not possible to

differentiate accurately between pneumococcal pneumonias and those of a viral origin. In the present study, pneumococci were isolated from the sputa or blood streams of approximately 70% of the pneumonia patients. Typing was done on pneumococci isolated from blood cultures.

*Dosage.* Two dosage schedules were employed. An initial 3 gm. by mouth was followed by 1 gm. every 6 hours in all except 22 patients. The latter received an initial dose of 6 gm., followed by 1 gm. every 6 hours. This deviation from the standard dose caused no perceptible improvement in response and was therefore abandoned. The average total dose of the successfully treated patients was about 32 gm. All patients received at least 2500 cc. of fluid during each 24 hour period, insofar as this was possible.

Examination of urine specimens for the presence of crystals of sulfonamide was made as described previously,<sup>1</sup> using the sediment separated by centrifugation from 50 ml. samples of urine. The sediment was suspended in 0.5 ml. of urine and a drop examined under the low power objective of a microscope. The specimens were examined 1 to 2 hours after being voided, being held in the interim in an incubator at 37° C.

**Results.** The response of the patients receiving the sulfonamide combination was superior to that observed when single sulfonamides were administered. This was manifested by a more rapid initial fall in temperature following administration of the drug and by an earlier return to normal temperature in the groups treated with combined sulfonamides (Fig.1). The differences are sufficiently large to make it unlikely that they are due to chance. Application of the chi square test gives statistically significant *P* values in both tabulations ( $P < 0.02$  and  $P < 0.01$ ) when the number of patients in the 2 groups showing initial temperature fall or normal temperatures respectively is compared. The difference between the mean number of days required for the initial temperature fall is just short of the usually accepted level of significance with  $P = 0.07$ . However, the corresponding difference for return to normal temperature is without significance.

Patients who did not do well on the sulfonamide therapy were given penicillin in addition, and the number receiving penicillin supplementation provides a further test of comparative effectiveness. Eight patients of the sulfadiazine treated (1946-1947) group were so supplemented out of a total of 107 (7.5%), as compared with 6.1% receiving the combined sulfonamides. This is not a significant difference, yet it suggests that the combination therapy was no less effective than sulfadiazine.

The average length of time required for treatment of pneumonia by means of the combined sulfadiazine-sulfamerazine preparation was 6.0 days, as compared with 6.3 days when sulfadiazine alone was used. Patients receiving supplementary penicillin were not included in this comparison. Six deaths occurred in the sulfadiazine treated group and 4 in the combined sulfonamide group, but, only 2 could be attributed to pneumonia, 1 in the sulfadiazine treated group and 1 in the sulfadiazine-sulfamerazine treated group. Each of these patients had received antibiotic therapy in addition to the sulfonamide. The others were the result of complicating disease, including tuberculous meningitis (2), meningococcic meningitis, alcoholism, and hypertensive cardiovascular disease (2), terminal renal disease, and rheumatic heart disease with terminal pulmonary infarct.

*Concentrations of sulfonamide in serum.* Administration of combined sulfadiazine and sulfamerazine gave an appreciably higher concentration in serum than did sulfadiazine alone. The average concentration during administration of the former was 14.4 mg. per 100 ml. (expressed as sulfadiazine), as compared with 11.3 mg. for sulfadiazine. Sulfamerazine is known to give higher concentrations in plasma than sulfadiazine. This would explain

in part the higher levels resulting from the combined drugs. Another cause is the omission of sodium bicarbonate as an adjuvant. Administration of the large amounts of sodium bicarbonate required to maintain an alkaline reaction in urine depressed the concentrations of sulfonamide in blood.<sup>1</sup> The smaller quantity of sodium bicarbonate used in treatment of some of the patients also had an appreciable effect on plasma concentrations, seen in the group of patients that received sodium bicarbonate (at the rate of 6 gm. daily) with the combined sulfonamides. The

as that observed in those receiving sulfadiazine with or without 6 grams of sodium bicarbonate daily. This amount of sodium bicarbonate is less than that found necessary to render the urine sufficiently alkaline to eliminate sulfonamide crystal formation,<sup>1,3</sup> however, we continue to remain in doubt concerning the advisability of giving large amounts of sodium bicarbonate to a group of patients that includes many with impaired cardiac reserve.

In the 1946 series, microscopic hematuria occurred in only 2 of 104 patients receiving combined sulfonamide

TABLE 1.—INCIDENCE OF CRYSTALLURIA IN 4 KINDS OF SULFONAMIDE THERAPY

|   | Total | Patients<br>Number with<br>crystalluria | Per cent | Total | Urine Specimens<br>Number with<br>crystals | Per cent |
|---|-------|---|----------|-------|--|----------|
| Sulfadiazine-<br>sulfamerazine<br>combination<br>6 gm./day    | 169   | 49                                      | 29.0     | 549   | 89   | 16.2     |
| Sulfadiazine<br>6 gm./day plus<br>6 gm. sodium<br>bicarbonate | 107   | 24                                      | 22.4     | 306   | 39   | 12.7     |
| Sulfadiazine<br>6 gm./day                                     | 32    | 11                                      | 34.6     | 60    | 17   | 28.3     |
| Sulfadiazine<br>6 gm./day                                     | 45    | 19                                      | 42.2     | 90    | 25   | 27.7     |

average concentration of sulfonamide in plasma was lower by about 10% in this group than in the patients not receiving the alkali.

*Crystalluria and urinary tract complications.* The use of a combination of sulfadiazine and sulfamerazine resulted in a decrease in the number of urine specimens containing crystals of the sulfonamides (Table 1). The incidence of crystals was higher than that observed initially,<sup>1</sup> but is less than that in the group receiving sulfadiazine or sulfamerazine without alkali. However, the number of patients receiving the combination who showed crystals in urine at some time was about the same

therapy, as compared with a rate of 5% in sulfadiazine or sulfamerazine treated patients. In the 1946-1947 series, erythrocytes and leukocytes were observed more frequently in urine sediments of the patients receiving the combination (13 of 65 patients) than in those obtained from the sulfadiazine treated controls (4% of the patients). The sediment contained from 2 to 20 erythrocytes per low power field, with more leukocytes than erythrocytes. Since the sediment examined was obtained by centrifugation of 50 ml. of urine, the number of cells present in the urine is small and we believe of minor significance. Furthermore, crystals of sulfona-

mide were detected in association with the cellular elements in only 6 of the 13. Finally, the apparently lower incidence of erythrocytes in the sulfadiazine treated controls is deceptive because the higher average pH of the urine specimens in this group resulting from bicarbonate supplementation would decrease their survival.

Microscopic hematuria of a degree that conformed to the usual clinical use of the term occurred only 3 times in the entire series of 169 patients receiving the sulfadiazine-sulfamerazine combination and 5 times in the 187 sulfadiazine treated patients. Gross hematuria was observed once in the former and once in the latter. The hematuria occurring in the patients receiving the combined drugs was associated with crystalluria only in 1 instance, while the reverse was true in the sulfadiazine treated group.

Five patients of the combination-treated group, in addition to the one with gross hematuria, had toxic reactions which were attributed to the sulfonamides and were considered indications for discontinuation of this therapy: in 1, severe vomiting occurred; another developed a leukopenia of 2800 cells per cu.mm.; 1 showed fever, attributed to the drug; 1 developed an ecchymotic rash, and 1 showed general signs of toxicity. The character and frequency of these toxic reactions did not differ from those encountered in the sulfadiazine treated control group.

**Discussion.** The present study supports the view that the use of a combination of sulfonamides offers advantages over the use of a single compound.<sup>1,2,4,5,7</sup> The hazard of mechanical injury to the urinary tract is decreased because the total amount of sulfonamide capable of being held in solution is increased when two or more sulfonamides are administered. The therapeutic response, as judged by fall

in body temperature, has been demonstrated in this study to be superior when a combination of sulfadiazine and sulfamerazine is administered to that obtained when sulfadiazine alone is used at the same dosage level. Previous studies have shown sulfadiazine and sulfamerazine to be about equally effective, hence the gain is not the result of a superiority of sulfonamide in blood when the combination is used, although the levels obtained were no higher than those obtainable using sulfamerazine alone. The higher concentrations in serum are due to the greater tendency of sulfamerazine to combine with serum protein and also are the result of omission of an alkaline adjuvant. Whether the interesting likelihood exists that the presence of the two sulfonamides increases the effective concentration in fluids within the body, just as it was shown to do in urine, remains to be established.

The low mortality observed with but a single death in each group is, in part, a result of auxiliary penicillin therapy used in pneumonia patients. A factor of selection also enters, in that patients who were gravely ill on admission, were treated at once with sulfonamides and penicillin, although elimination of these patients would have little influence on the comparison that is the subject of this paper. Also, the greater frequency of viral pneumonias in recent years is contributory.<sup>3</sup>

Zeller, Hirsh, Sweet, and Dowling<sup>9</sup> found fever, rash, or conjunctivitis to be more prevalent when a sulfadiazine and sulfamerazine mixture was used in treatment of meningitis, compared with the incidence when sulfadiazine or sulfamerazine alone was used. The incidence of these toxic effects has been low in our series and did not differ from that encountered in the controls receiving sulfadiazine. The dosages used by Zeller and associates<sup>9</sup> were considerably greater than those em-

ployed in the present study and this may provide an explanation for the differences. It should be noted that Zeller and associates attribute all of the increase in toxicity to the use of mixed sulfonamides, without assigning any of the responsibility to the higher dosage and blood concentrations in their mixture treated groups. Objections to their conclusions have been offered by Lehr.<sup>7</sup>

Since the studies described in this paper were completed, trial of combinations containing a third sulfonamide, namely sulfathiazole, sulfamethazine, or others, in addition to sulfadiazine and sulfamerazine, has indicated that the occurrence of crystalluria can be decreased to negligible proportions. The superiority of the triple combina-

tions in this respect suggests that they may eventually replace the double combinations studied in this paper.

**Conclusions.** 1. The use of a sulfadiazine-sulfamerazine combination, without concomitant alkali therapy, in a series of 169 patients with a diagnosis of pneumonia resulted in a lowered frequency of sulfonamide crystals in urine approaching that observed when sulfadiazine was supplemented with sodium bicarbonate at the rate of 6 gm. daily.

2. The therapeutic efficacy of the sulfonamide combination observed in the treatment of 149 patients was equal to and in some respects was superior to that of sulfadiazine alone in a control group of 107 patients.

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# PROGRESS OF MEDICAL SCIENCE MEDICINE

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## HYPOTENSION

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ALTHOUGH it is not possible to cover every aspect of any one disease in a review of this kind, the purpose of this paper is to present some of the physiologic and clinical advances concerning "low blood pressure" and to correlate these physiologic considerations with clinical symptomatology, related diseases and management. Shock, an abnormal physiologic state associated with hypotension, will not be discussed in this presentation.

**Definition.** The definition of *hypotension* as employed by various investigators varies according to their respective standards. Studies which indicate an incidence of "hypotension" in normal and healthy people should be viewed cautiously. Blood pressure, like any other biologic phenomenon, has a normal distribution or Gausserian curve. Variations are considerable among a large group of normal people and also from time to time within the same individual. A person who has no symptoms may have extremely "low blood pressure" and still be free from any disease. The problem becomes clinically significant only when dis-

ease is suspected because of other manifestations. It is hoped that these various difficulties will become evident as this review progresses.

Thus far in the 53 years since Riva-Rocci applied the rubber cuff to the mercury manometer or since Korotkow demonstrated the advantages of auscultation over palpation, the limits of "normal" blood pressure have not been established. The more common errors of the method which may cause inaccurate, low readings include: (1) failure to exceed the auscultatory gap, (2) too rapid deflation of the cuff, particularly in the presence of bradycardia, (3) leakage of mercury from the apparatus with an initial level below zero, (4) failure to place the apparatus on a surface level with the observer's eye, resulting in parallax errors, (5) improper placement of the bell over the artery, (6) changes in calibration of the aneroid-type manometers, and lastly (7) improper positioning of the subject's arm<sup>20</sup>.

The boundary for the lower level of normal systolic blood pressure has been decreased from 120 to 115 to 110 mm.

of mercury; the last of these is generally accepted, primarily because of precedence. Some have ventured to still lower levels of 100<sup>82</sup> or 90<sup>4</sup>. The United States Army Air Force set 105 as the lower limit of normal prior to 1936<sup>117</sup> but later this was changed to 100<sup>105</sup>. At the same time the Royal Air Force established the lower limit as 110.

The uncertainty of what the lower limit of normal arterial pressure should be is exemplified by Robinson<sup>102</sup>, who in 1939 studied 10,833 individuals and established the normal range as 90 to 120/60 to 80; in 1940<sup>101</sup>, however, he chose 110 as the arbitrary boundary for the systolic pressure because one-half the previous writers had selected that level. Roberts<sup>100</sup> wrote in 1922 that hypotension was one of the indefinite problems of medicine and that the upper limits of the systolic pressure of hypotension ranged from 100 to 125; he cautiously chose 110 as his dividing line. The most recent textbooks of medicine set the upper limits of hypotension as 110/70. It should be emphasized that regardless of the level of blood pressure, relative hypotension may exist, *i. e.*, the reading may be definitely below the usual one for that individual, even though it may be considerably above "normal" levels<sup>96,100</sup>.

**Incidence.** Early statistical studies of blood pressure revealed that 3.5% of persons in good health had "hypotension" according to the definitions of Alvarez<sup>5</sup> and Barach<sup>8</sup>. In 1939 a study of an urban population indicated that 25% of 11,000 people had systolic levels below 110 and 34% had diastolic pressures below 70. Only 4.5% of the men and 1.7% of the women had systolic pressures under 90, and only 2 men and 4 women examined had systolic pressures below 80 mm. of mercury<sup>102</sup>. A study of bank clerks and other sedentary workers showed that 38% of the men and 58% of the women, whose ages ranged from 17 to 30 years, had

hypotension<sup>99</sup>. Johnson<sup>66</sup>, selecting 110 and 140 as the limits of normal, reported that only 32% of his patients had normal blood pressure; in 31% the pressures were too high and in 37% too low.

Robinson<sup>102</sup> suggested that statistics on blood pressure released by insurance companies were not valid because of a tendency for physicians to "round out" a figure within the acceptable level for any particular year. As soon as the lower level of 100 was accepted by the insurance companies, the frequency of lower readings increased, and later when 90 was acceptable, the incidence of still lower readings increased. Few physicians would deny an individual insurance on the basis of a deviation of about 5 mm. of mercury in a routine examination. This same statistical lowering of levels for blood pressure appeared in the records of young men examined for duty in the Air Force<sup>55,105</sup>. Although no recent statistical review of insurance records has been made, it is likely that the concept of average normal blood pressure has decreased considerably and that the generally accepted boundary of hypotension must be dropped to remain below the rapidly changing "limits of normal." The most recent available survey of the blood pressures of a large number of people is a report in 1917 based on the records of 43,800 men and 31,458 women, mostly young university students in the United States<sup>14</sup>. Of the men 2.36% and of the women 15.98% had systolic pressures below 100, and 11.69% of the men and 30.22% of the women had pressures between 100 and 109. Previous definitions of hypotension as a systolic pressure below 110 would include about one-half of the women and one-seventh of the men of this series.

The incidence cited above prevails in the United States and Great Britain, but levels considered hypotensive in



these countries might well be "normal" for natives of many other geographic locations. No statistical data are available on the incidence of relative hypotension.

**Mechanisms.** The actual fundamental factors concerned with reduction in blood pressure are: (1) decrease in circulating blood volume, (2) decrease in peripheral resistance, (3) decrease in cardiac output, (4) increase in size of the vascular bed or (5) decrease in viscosity of the blood. Although each of these factors may be controlled by other variables, there is considerable interdependency among them. In any individual one factor may be of primary importance. Specific initiating factors are numerous, as indicated below. One or more of the above 5 fundamental phenomena are concerned with a decline in blood pressure in either health or disease whether or not the level decreases acutely or is persistently low.

**General Physiologic Factors.** Some general factors which have been thought to influence the blood pressure of man affect the physiologic mechanism in a general manner. Their action is not clear but deserves mention.

**Geographic influences.** Whereas the actual cartographic habitat of a person has little to do with his blood pressure, his way of life, diet and physical and emotional customs may have great influence. It has been shown that the average blood pressure of some peoples is much lower than that of others<sup>69</sup>. Although Eskimos have about the same levels of blood pressure as Americans in the United States<sup>40</sup> and lower blood pressures are found in people living in India<sup>83</sup>, Central America<sup>67,68,114</sup>, West Indies<sup>7,103</sup>, China<sup>12,71,131</sup>, along the Euphrates<sup>63</sup>, or in the Australian desert<sup>91</sup>, this cannot be attributed to climate according to Lemann<sup>76</sup>. However,

others<sup>10,45,103,115,124</sup> contend that climate does play a part in maintaining lower blood pressure.

Sociologic explanations for variations in blood pressure have been proposed. Kean<sup>67</sup> pointed out that whereas Negroes in Africa have relative hypotension, Negroes in the United States, particularly in the South, have hypertension. Likewise, the West Indians in Panama have higher levels of blood pressure than native Panamanians, among whom there was a greater incidence of hypotension. The environmental strain inevitably imposed upon a "foreign" minority appears to produce elevated blood pressure. In contrast, it has been suggested that the completely communistic form of life of the Australian aboriginal<sup>91</sup> and the low tone of physical, mental and nervous activity of the Arab<sup>63</sup> relieve them from the strain of civilization and spare their cardiovascular systems the burden of associated competition and resultant tension.

**Environmental Temperature.** Studies on the effect of increased environmental temperature upon blood pressure indicate that temperature and humidity associated with seasonal variations have little influence on blood pressure<sup>47,76</sup>. Experiments with ultraviolet irradiation produced no change in blood pressure. Gottlieb<sup>51</sup> detected no change with more rapid but mild elevations in environmental temperature. Studies of circulatory changes at high temperatures disclosed that though diastolic pressure may fall, there is an early rise in systolic pressure with increased pulse rate accompanying capillary dilatation. The peripheral blood vessels continue to dilate, decreasing resistance with pooling and reducing the return of blood to the heart. Eventually, despite the compensatory tachycardia, return of blood to the heart becomes inadequate and circulatory failure or shock is complete<sup>2</sup>.

*Heredity.* Some workers have speculated that hypotension might be an inherited characteristic<sup>45,128</sup>. Garvin's<sup>49</sup> report of 6 cases of hypotension in one family supports this idea; but without an understanding of the influence of environment, temperament, diet, and other factors, this observation cannot be accepted as proof.

*Exercise.* As early as 1895<sup>61</sup> the effects of exercise on blood pressure were studied. In 1922 Schneider<sup>110</sup> and Addis<sup>1</sup> reported separate studies indicating that blood pressure increases with exercise, whereas Gambill<sup>48</sup> in 1944 reported that exercise of an extremity reduced diastolic pressure but had little effect on systolic pressure. This he attributed to local release of vasodilating substances. Thacker<sup>128</sup> in 1940 discovered an increase in blood pressure after exercise in normal, hypertensive and hypotensive individuals. In the 2 abnormal groups there was slower response and slower return to normal. He concluded that vasomotor response from other factors plays a more important role in increasing systolic pressure than does pulse rate and that the same factors which govern the emotional status of the individual are influential in the rise in systolic pressure accompanying exercise. When the mechanisms which govern vasomotor response fail, then postexertional hypotension, possibly orthostatic in nature, will manifest itself<sup>33</sup>. There appears to be pooling of blood in an extremity, since maneuvers designed to move blood out of that part prevent the hypotensive reaction.

*Fatigue and Sleep.* When severe exertion results in fatigue, a fall in diastolic and systolic pressures ensues<sup>85</sup>. After prolonged rest these return to the previous levels. Depressed physiologic function of the endocrinologic and nervous systems as well as a generalized decrease in muscular tone are believed to be the mechanisms respon-

sible for the decline. The latter is said to account for the reduction during sleep<sup>10,45,85</sup> and hypnosis<sup>41</sup>. Tone has been defined by Dorland<sup>28</sup> as "the condition of tension of normal muscles which exists independently of voluntary innervation."

*Fever and Inflammation.* Blood pressure may rise or fall during development of fever<sup>3</sup>. Often no change is noted during prodromal states<sup>112</sup> but occasionally there is a rise during a chill due to vasoconstriction. Since the level of blood pressure is a reflection of the state of constriction of the blood vessels on one hand and of a variable decrease in cardiac output on the other, if the latter is great, hypotension develops despite vasoconstriction. During the flush phase of vasodilatation blood pressure drops.

The strain placed upon the vasomotor regulatory mechanism in prolonged or repeated febrile episodes may account in part for the commonly encountered postinfectious state characterized by vasomotor or cardiomotor instability, hypotonus and concomitant lowering of blood pressure<sup>3</sup>. Taylor and Page<sup>126</sup> discredit fever and leukocytosis as a cause for a diminished blood pressure following nonspecific inflammatory processes. They suggest that inflammatory reactions impair function of the adrenals, which in turn may effect a reduction in blood pressure.

*Nutrition.* Dietary management of high blood pressure is now popular. The mechanism of the rice diet has not yet been established, although a reduction in protein<sup>70</sup> or sodium metabolism<sup>73,111</sup> is thought to be an important factor. If Nye<sup>91</sup> had advocated the dietary habits of the Australian aboriginal as a means of lowering blood pressures, then hypertensive Americans would today be gorging themselves with game meat for several consecutive days and then abstaining

from food for several more. He suggests that the products of protein metabolism may possibly be completely eliminated during the periods of fasting. Also there is little salt in the food of these people as well as in the fruit diet of the Cuna Indians of Panama<sup>68</sup>. Shattuck<sup>114</sup> suggested that the low blood pressure of the Guatemalan was possibly due to a deficient diet.

That starvation diets and diets inadequate in protein depress blood pressure is further supported by reports of observations on starving Europeans and prisoners of war<sup>77,78</sup> and of planned experiments on volunteers at the University of Minnesota<sup>125</sup>. The increasing incidence of tuberculosis and other diseases among the starving Europeans may have played a role in the decline in the average levels of blood pressure. Psychic or emotional factors cannot be completely excluded in these studies. During the period of anxiety prior to starvation, levels of blood pressure were highest; when the starvation period was in effect and hostile occupation forces were suppressing the peoples so that all hope was abandoned, hypotension became most prominent. With renewal of hope and resumption of the problems of competitive living, the average blood pressure became elevated again.

Other cachectic states, such as anorexia nervosa or Simmond's disease, are associated with hypotensive pressures which are not as extreme as those seen in Addison's disease. It is difficult to separate the influence of the generalized psychic depression from that of depression of endocrinologic systems. Regardless of the initiating factor, severe undernutrition in rats results in a physiologic pattern resembling that of the hypophysectomized animal<sup>90</sup>. The caloric deprivation and reversible pituitary depression in man is accompanied by decreased adrenal cortical activity<sup>125</sup>. This is also true of the other

endocrine glands which are concerned with maintenance of fluid and electrolyte balance, blood pressure, vasomotor stability and muscular tone.

The role played by vitamin deficiency is unsettled but in the cardiac type of beriberi, the blood pressure may be normal or low<sup>119</sup>. Rats with vitamin E deficiency have been shown to have blood pressures 29% lower than nondeficient controls<sup>127</sup>.

**Specific Physiologic Phenomena.** There are physiologic phenomena which are more specific in their role in the regulation of blood pressure than those just described. Some of the more important ones are presented.

*Reflex phenomena.* Certain reflex phenomena are concerned with regulation of arterial blood pressure. Although they are probably related to some extent to all forms of hypotension and all specific mechanisms, some aspects of their role deserve separate consideration. Heymans<sup>60</sup> and Bronk<sup>17</sup> discuss in detail the pressoreceptive mechanisms which regulate cardiac rate, vasomotor tone, and blood pressure. Pressosensitive areas are situated in the carotid sinus and the venoauricular, pulmoarterial and thoracosplanchnic areas. They are reflexogenic and react to changes in intravascular pressure so that when the pressure increases, reflex vasodilatation and cardiac slowing occur with diminution in cardiac output. The reverse occurs with a decrease in intravascular pressure in these areas. In many other vascular areas local vasomotor reactions take place. The normal organism is able to compensate for sudden transient changes in blood pressure invoked by a disturbance in one of the fundamental factors, but if the reflex proprioceptive regulators become depressed or paralyzed, then compensatory power is lost. Some of the causes may be acute, such as trauma to the areas. severe anoxemia, including that pro-

duced by hemorrhage, spinal anesthesia, deep general anesthesia, administration of barbiturates, morphine or other narcotics, hypocalcemia produced by injection of citrate or oxalate or parathyroidectomy, pulmonary hyperventilation, histamine, ergotamine or the dioxane-like substances. With the regulating mechanism depressed, permanent fall in pressure results from some initiating stimulus, and circulatory collapse follows.

More subtle depression of the regulatory centers which protect against extreme variations of blood pressure may permit persistently lower or higher levels, depending on the nature of the stimulus. These physiologic phenomena are made more complex by the relation between the mechanisms regulating blood pressure and those adapting the peripheral circulation to nutritional needs of the tissues and organs. Vessels dilated to meet local metabolic demand do not undergo nervous or adrenergic vasoconstriction.

It should be pointed out that suprarenal and neurovascular reflex regulators of the blood pressure may act independently. The zone of the carotid sinus, when the carotid body is included, is chemosensitive as well as pressosensitive, so that changes in oxygen or carbon dioxide or the presence of one of several drugs in the blood can influence the centers and modify the blood pressure<sup>60</sup>.

Although the arteries of the central nervous system are not thought to participate actively in the general reflexive regulation of blood pressure, the cerebral blood supply is constantly dependent upon the general systolic arterial pressure, which is regulated by the aorta and carotid sinus<sup>13</sup>. In cases of decreased systolic arterial pressure, peripheral and splanchnic vasoconstriction deviate blood into the cerebral circulation.

Reflex syncope may follow the occur-

rence of transient hypotension in persons with a hyperactive carotid sinus reflex<sup>37,46,116,134,135,137</sup>. Three types of carotid sinus syndromes are described: (1) cardiac inhibition, (2) vasodepression, in which a sharp drop in blood pressure may occur without cardiac inhibition and, (3) the cerebral type, with no fall in blood pressure. The fall in blood pressure usually occurs at the time of syncope, and as a rule bradycardia is present. These physiologic reactions do not occur if the carotid area is denervated<sup>137</sup>. Anatomic enlargement of the carotid sinus has been reported in the hypersensitive individual<sup>37,137</sup>. Syncope has been attributed to cerebral anoxemia produced by asystole and fall in arterial blood pressure<sup>46</sup>.

Vasodepressive syncope is seen in conditions other than the hyperactive carotid syndrome. Stimulation of the arterial wall, not associated with pain and not related to psychic factors, has been shown to produce peripheral vasodilatation, tachycardia, considerable fall in blood pressure and collapse in one-third of the individuals tested in this manner<sup>105</sup>. Syncope associated with venipuncture and accompanied by reduced blood pressure is often encountered in blood donors and has been attributed to psychic influences<sup>59</sup>. In reporting syncope and fall in blood pressure accompanying exertional dyspnea and angina pectoris, Golden<sup>50</sup> suggested that the heart was unable to increase the cardiac output during exertion or to increase its output in response to reflexes arising from engorged lungs or an ischemic myocardium.

It has been suggested that stimulation of the arch of the aorta might be a factor<sup>12</sup> in the hypotension occurring during thoracic surgical operations. It was concluded, however, that alteration of blood pressure was due to mechanical impediment of blood flow to the

heart by compression of vessels. Because this would also increase intravascular pressure, the presence of a reflexogenic pulmoarterial area was suggested which might be concerned with the hypotension.

Local increases in pressure are thought to play a large part in the lowering of systemic pressure in pulmonary arterial occlusion<sup>55</sup>. The extreme constriction of the entire pulmonary vascular bed, which impairs the pulmonary flow of blood, diminishes the output of the left ventricle, producing a decline in arterial blood pressure. Atropine and papaverine have been said to relieve this vasoconstriction dramatically and to permit restoration of the cardiac output<sup>27</sup>.

Penetrating wounds of the chest<sup>86</sup> may reduce the blood pressure by afferent impulses arising in the pleura which produce arteriolar dilatation.

*Postural maladaptation.* The relationship of posture to blood pressure was studied as early as 1895<sup>61</sup>, but it was not until 1925, when Bradbury and Eggleston<sup>15</sup> reported their cases of postural hypotension, that it was regarded as a disease entity. The physiologic adaptations concerned with adoption of the erect posture and relation to gravity has since received much study. Factors operating to maintain blood pressure in the erect posture are discussed in recent reviews<sup>92,120</sup>; they are essentially (1) peripheral vasoconstrictions, (2) acceleration of the cardiac rate, and (3) greater tonus of skeletal musculature. The compensatory mechanisms are not simple and not agreed upon generally.

There has been lack of agreement as to the mechanism for the reduction in pressure. Ellis and Haynes<sup>34</sup> suggested that it was due to greater than normal pooling of blood in the lower extremity. MacLean, Allen and Magath<sup>89</sup>, by use of the Flack test, asserted that failure of adequate return of venous blood to

the heart is an essential factor in the syndrome of orthostatic hypotension. This test consists in increasing intrathoracic pressure of the subject by forced exhalation against a column of mercury and measuring the length of time the pressure can be maintained. Experiments employing tourniquets and tilting in normal subjects and in persons with postural maladaptation indicated that there was no more pooling in the lower part of the body in a maladapted individual on standing than in a normal individual but that the reflex vasoconstriction which maintained the pressure in a normal individual did not occur in these patients. This lack of adequate reflex vasoconstriction in the face of a decline in pressure is a fundamental disturbance in postural hypotension and suggests that it is a disorder of the sympathetic nervous system<sup>122</sup>. Absence of sweating, loss of libido, and other clinical manifestations of the syndrome tend to support this concept. These findings are not necessarily incompatible with the concept of reduced venous return, since the defective vasoconstriction probably gives rise to diminished venous return<sup>92</sup>.

From a study employing tagged erythrocytes Nylin<sup>92</sup> concluded that circulation is abnormally slow in the erect posture in postural maladaptation. This was indicated by the fact that even distribution of the tagged cells required more time in patients with postural hypotension than in normal subjects. Kvale<sup>74</sup> also showed that there was a larger increase in the arm-to-tongue circulation or arm-to-foot time in subjects with orthostatic hypotension following sympathectomy.

There are differences of opinion concerning the cardiac rate in postural hypotension. Some observers<sup>15,16,31,43,122</sup> have reported no change, whereas another<sup>26</sup> found an increase in the rate. Obviously, therefore, there may or may

not be a change in cardiac rate depending upon the activity of the cardio-accelerator reflex mechanism<sup>65</sup>. Functional disorders with associated postural hypotension in particular are apt to be accompanied by "orthostatic tachycardia"<sup>54,75,80,81</sup>. The electrocardiogram has not been found to be abnormal<sup>56,92</sup>.

Although the clinical conditions with associated postural maladaptation may be numerous, investigators agree that lesions of the sympathetic nervous system<sup>15,31,122,144</sup>, probably in the region of the hypothalamus<sup>11,92</sup>, are most often the initiating cause. This obviously does not include cases associated with local lesions of the sympathetic nervous system or patients who have had sympathectomies<sup>20,56,95,106</sup>. In the latter hypotension is usually relative and not absolute.

*Biochemical influences.* Anderson and his associates<sup>6</sup> induced fainting and lowering of blood pressure by administration of 7 to 8% oxygen, which produced active vasodilatation in the skeletal muscle and a decrease in cardiac rate. On the other hand, hyperventilation with excessive loss of carbon dioxide will cause lowering of the blood pressure in animals<sup>121</sup>. This is true for man as well<sup>64,118</sup>. It has recently been demonstrated that administration of carbon dioxide will prevent the "blackout" associated with centrifugal forces. This action is presumably through increased activity of the carotid sinus and resultant increase in muscular tone and decrease in the quantity of venous pooling<sup>132</sup>.

The exact role of electrolytes in maintenance of blood pressure remains unknown. It is probably related to the endocrinologic system. There is decreased concentration of blood chlorides caused by the increase in urinary excretion in pulmonary disease, for example, pneumonia, tuberculosis and carcinoma of the lung<sup>141</sup>. Adrenal

dysfunction may be present in these diseases, though no consistent abnormal pathologic finding has been described. The sodium content of the serum does not vary as greatly as the chlorides, the differences being accounted for by compensatory changes in bicarbonate. Low sodium and chloride content of serum observed as a result of the treatment of congestive heart failure and chronic renal disease with depletion of salt<sup>130</sup> are frequently accompanied by shock-like states<sup>97</sup>.

*Psychic factors.* Influence of the psyche on the cardiovascular system is difficult to evaluate and is for the most part still a matter of impression. Engle<sup>36</sup> and Romano<sup>104</sup> attempted to differentiate between vasodepressor and hysterical fainting by use of the electroencephalograph. Kremer<sup>73</sup>, who stimulated the cortex by acetyl-beta-methylcholine or faradic current, was able to localize areas which would produce lowering of blood pressure in dogs. The relationship of organic lesions of the nervous system to regulation of blood pressure has been indicated.

Most observers agree that functional disorders are related to the development of hypotension. The strenuous daily activities of civilization serve as stimuli which tend to maintain an increased "tone" of the physiologic systems. When people lack these stimuli or become psychically disturbed so that the pressure of the physiologic systems fails to be properly influenced by the conscious and subconscious levels, the blood pressure declines below the *average* for the "civilized" world or for the psychically normal person but it is not necessarily below *normal*. In severe depressive states the "tone" of the system is decreased and "hypotension" becomes manifest.

*Drugs.* The vasodilating effect of the nitrite group of drugs, with subsequent lowering of the blood pressure, is well known, the mechanism dealing pri-

marily with peripheral vascular dilatation<sup>138,140</sup>. Similar effects noted with acetylcholine and nitroglycerin are not completely inhibited by adrenal demedullation or cardiac denervation<sup>58</sup>.

Hypotension has been said to be produced by histamine or histamine-like substances, an idea particularly prevalent today because of increased interest in antihistamine drugs<sup>44,45</sup>. Carnosine, related to histidine and of unknown metabolic significance, present in mammalian muscle, has been shown to have severe depressive action on the blood pressure<sup>139</sup>.

Many agents used in therapy will induce a transient decrease in blood pressure. Some, such as plasmochin, act upon the central nervous system to depress sympathetic activity and produce hypotension<sup>88</sup>. Pentaquine (SN-13276), another antimalarial drug, will produce postural hypotension which may last for months<sup>25</sup>. Page<sup>94</sup> reported a case of poisoning with arsenic trioxide in which there was a mean pressure of 30 mm. of mercury with no ill effects. Other drugs which have been reported to reduce the blood pressure are cinchophen, bismuth subnitrate, and intravenous quinidine<sup>45</sup>. Connell<sup>21</sup> showed that there was no relation between blood pressure and the levels of thiocyanate naturally occurring in the blood.

**Interrelationship of all physiologic factors.** In summarizing factors related to internal and external environment which alter or maintain blood pressure, we must remember that social surroundings of an individual influence his emotional state, that his reactions will depend upon early training and possibly on heredity, that starvation cannot be considered separate from depression of the psyche or of the endocrinologic systems, that diet and electrolytic metabolism and their relation to endocrinologic or nervous functions influencing the cardiovascular

systems are inseparable. We may say, therefore, that inanition, whether due to starvation or to illness, probably exerts a depressing influence on bodily "tonus," endocrinologic function, and reactivity of reflexogenic centers; psychic disturbances manifest themselves by depressing general bodily reactions and tone or by stimulating or depressing certain reflex centers; deprivation of electrolytes (sodium and chloride) perhaps has its influence on blood volume or on the adrenal cortical regulators; and special cardiovascular governors manifest themselves in loss of constrictor power, cardiac inhibition, or failure of cardiac compensatory mechanism. We may also conclude that there is an undetermined interrelation among these factors which ultimately display failure of one or more of the physical mechanisms for maintaining blood pressure, namely: (1) blood volume, (2) peripheral resistance, (3) cardiac output, (4) size of the vascular bed and (5) viscosity of the blood.

**Influence of hypotension on certain organic systems.** When the mechanisms which tend to maintain adequate flow of blood to the brain are fatigued or dysfunctioning or when there is sudden fall in blood pressure, anoxia of the higher centers ensues. Though the effects of hypotension on mental and physical efficiency have not been established by objective methods, impairment of cerebral function was suggested in a study of fatal air crashes, considered to be the result of errors of the pilots. Seventy-three % of these pilots exhibited some form of hypotension<sup>143</sup>.

In spite of coronary vasodilatation with decreased resistance, hypotension is associated with decreased coronary flow<sup>93</sup>. Circulatory collapse, often associated with severe hypotension, may persist despite return of coronary flow to normal. Eckenhoﬀ<sup>32</sup> reported that he observed in dogs a decline in blood

pressure accompanied by decreased cardiac efficiency although there was no evidence that the heart was less able to accomplish the work demanded of it. Left ventricular work was reduced 56% and cardiac output 42%, with 29% decrease in coronary flow. These experiments failed to reveal that certain types of hypotension are harmful to the heart.

With a decrease in cardiac output or fall in arterial pressure, the rate of renal plasma flow is lessened; but the exact mechanism for the decline is still unsettled. Investigators believe that the flow through the kidney is diminished because of the decrease in pressure head and the other physiologic phenomena associated with some of the hypotensive states, for example, increase in viscosity of the blood, pooling of blood in the venous system, liberation of humoral vasoconstricting substances which produce afferent arteriolar constriction of the glomerular tufts<sup>23,24</sup>. When there is extreme diminution of blood flow to the kidney accompanying severe hypotension, urinary output ceases. In subjects with postural hypotension decreased urinary flow during the day is followed by compensatory nocturia.

Pepper<sup>26</sup> is of the opinion that the onset of hypotension, absolute or relative, predisposes to formation of arterial thrombi, particularly in people with arteriosclerotic disease and roughened arteries which impair blood flow. The increase in viscosity of the blood associated with the hemoconcentration often encountered in hypotensive conditions<sup>18</sup> also predisposes to impairment of flow and formation of thrombi.

General health is not unfavorably affected by hypotension<sup>30,55,52,100</sup>; in fact life expectancy has been found greater in the presence of low blood pressure<sup>44,62</sup>. Hypotension seems to preserve rather than injure the physiologic system. After the age of 50, things be-

ing otherwise equal, hypotension may be interpreted as a sign of an efficient and healthy cardiovascular renal system<sup>85</sup>.

**Clinical Picture.** The clinical picture associated with hypotension varies with the rapidity and degree of reduction in blood pressure. A sudden fall, regardless of previous levels, is manifested by symptoms of giddiness, faintness, and loss of consciousness, all of which may be attributable to cerebral anoxia.

However, if chronic, sustained hypotension is associated with symptoms, the clinical picture is different. It should then be understood that hypotension itself is but one manifestation of the primary disorder which is responsible for the multitude of associated symptoms, such as generalized weakness, fatigue, dizziness, fainting, gastro-intestinal complaints, belching, flatulence, palpitation, insomnia, numbness in the extremities and many others. It is apparent that such nonspecific symptoms will be encountered in hypertensive and normotensive subjects as well. Anhidrosis, impotence, and nocturia are additional manifestations of postural hypotension.

As is true of symptoms, observations made on physical examination and laboratory data are dependent upon the primary disorder. In asymptomatic essential hypotension there will probably be no constant associated signs. These individuals are likely to be well adjusted and well developed and to have no abnormal physical findings. A particular physical type has come to be associated with hypotension occurring simultaneously with other symptoms. Although obesity, not to be confused with hypersthenia<sup>19</sup>, may be accompanied by low blood pressure, the hypotensive individuals fall into the linearly built, underweight class about twice as often as in the laterally built, overweight group<sup>70,101</sup>. The habitus and



accompanying signs should not condemn a patient categorically as a constitutionally inadequate individual.

The body temperature of many patients of both the asthenic group<sup>98</sup> and the essential hypotensive class is lower than that of other individuals. In hypotension the pulse is variable. Of diagnostic value is the finding that in postural hypotension with absence of sweating the skin is dry, whereas in the neurasthenic patient it is moist. Hypotensive individuals frequently have narrow nostrils and nasal obstruction, decreased thoracic capacity, and often signs of asthma<sup>8,10</sup>. Manifestations of enteroptosis are usually found even in the presence of obesity.

Frequently associated with postural and essential hypotension are anemia, low basal metabolic rate, reduced gastric acidity<sup>72</sup>, low blood sugar<sup>9</sup>, low blood chloride<sup>10,141</sup>, and blood urea nitrogen at the upper limit of normal or slightly elevated<sup>99</sup>. Roentgenographic examination of the asthenic hypotensive subject reveals the arch of the aorta to be small, the heart to be vertically placed and together with the great vessels to appear elongated<sup>10,12</sup>. There are no significant electrocardiographic abnormalities.

**Clinical Conditions Associated With Hypotension.** The conditions provoking or associated with hypotensive levels of blood pressure are legion. Some of these will be listed and a few of the most important will be discussed. For the sake of organization, a modification of Stieglitz's<sup>121</sup> clinical classification will be used.

*Acute fall in blood pressure* occurs in shock, medical or surgical; food poisoning; fright; during or after administration of anesthetics, vasodilating drugs or poisons; anaphylactic reactions<sup>44</sup> and pulmonary embolism<sup>27,53</sup>.

*Subacute hypotension* is associated chiefly with infectious diseases. Typhoid, scarlet fever, typhus, influenza,

malaria, trichinosis, pneumonia, and cholera<sup>8,10,44,45,99</sup> all produce hypotension as a result of dehydration, fever, electrolytic imbalance, lowering of bodily tonus and some degree of myocardial weakness. In pneumonia early severe fall in blood pressure is of serious prognostic significance, comparable to absence of leukocytosis in this disease<sup>10</sup>. There may be prolonged hypotension following convalescence. Renal disease<sup>130</sup> in some stages, when accompanied by loss of electrolytes, diabetic acidosis, or peptic ulcer<sup>96</sup>, may also provoke lowering of blood pressure. The initial fall seen after myocardial infarction has been ascribed to peripheral circulatory collapse of reflex origin and to forward failure consequent to left ventricular infarction<sup>87</sup>. Persistent low pressures for 3 to 5 days indicate a poor prognosis. Most surviving patients with previous hypertension have a return of blood pressure to hypertensive levels after one year<sup>44,87,95</sup>.

*Chronic hypotension*, besides being an integral part of the hypotonic, hyporeactive state<sup>72</sup>, is associated with the chronic endocrinopathies, anemia, and chronic infectious diseases. It is one of the diagnostic criteria for Addison's disease<sup>55,129</sup> and is a common accompaniment of Simmond's disease and hypothyroidism<sup>41,99</sup>. Hypoplasia may exist with certain constitutional states involving a decrease in muscular or vascular tone, such as myasthenia gravis, status lymphaticus<sup>10,99</sup> and myotonia atrophica<sup>39</sup>. The systolic pressure may be as low as 60 to 80 mm. of mercury in pernicious anemia<sup>10,41,99</sup>.

Chronic focal infections and toxemias are frequently accompanied by hypotension<sup>10,41,45,99</sup>. Decrease in the tone of the skeletal, smooth and myocardial muscles and toxic depression of the endocrine glands and of the sympathetic control of the vascular tone are suggested mechanisms. The possible influences of toxic products, such as sub-

stances like histamine<sup>44,99</sup> or carnosine<sup>130</sup>, must be considered.

Association of hypotension with tuberculosis has been reported since the early days of the mercury manometer. In 1911, Emerson<sup>35</sup> presented a comprehensive review of this subject, stressing the diagnostic and prognostic value of hypotension in tuberculosis. His experimental work indicated a possible toxic mechanism acting on nearly all the organic systems, particularly the vasomotor regulating centers. Subsequently, no comprehensive study which definitely indicates that the incidence of hypotension is higher in patients with tuberculosis than in the general population was found in the literature of the English-speaking countries. Nearly all discussions of hypotension include tuberculosis as one of the important causes<sup>10,41,44,45,85,90,105</sup>, however, and associate it with activity of the disease<sup>142</sup>. Tuberculosis of the adrenal glands is thought by many to be the cause of the hypotension, but the latter is sometimes present even in the absence of the former. Loss of tone, psychic depression, and chloride imbalance undoubtedly play some part. Much emphasis has been placed upon the inter-relation between hypotension and tuberculosis, but this has not been substantiated by facts.

From the list of clinical conditions associated with *postural hypotension*<sup>120</sup>, it is obvious that this is not itself a clinical entity but is merely a manifestation of the disturbance in reflex control of the cardiovascular system. Diseases of the nervous system which have been reported to effect this disturbance are: combined sclerosis of pernicious anemia, disseminated sclerosis<sup>80</sup>, syringomyelia, arteriosclerotic degeneration disseminated throughout the nervous system<sup>84</sup>, multiple encephalomalacias<sup>57</sup>, Parkinsonism<sup>92,144</sup>, Ménière's syndrome<sup>96</sup>, influenzal encephalitis<sup>75</sup>, tabes dorsalis<sup>80</sup>, dementia paralytica<sup>43</sup>, sym-

pathetic ganglionectomy in treatment of hypertension<sup>56,80,106</sup>, diabetic neuropathy<sup>107</sup>, diabetic neuritis<sup>80</sup> and psychic disturbances. Endocrinopathies which may be associated with this disturbance are thought to produce changes in the cells of the hypothalamus<sup>11</sup>, hypoinsulinism, hypopituitarism<sup>80</sup>, diabetes insipidus, exophthalmic goiter<sup>80</sup> and Addison's disease<sup>11</sup>. Postural maladaptation is also observed in myasthenia gravis<sup>81</sup>, peptic ulcer<sup>109</sup>, sprue<sup>80</sup> and in a high percentage of dermatologic patients<sup>133</sup>.

**Management.** Since hypotension is not a disease entity, it should not be managed as such. Essential asymptomatic hypotension discovered on routine examination warrants investigation to determine whether it is a manifestation of some underlying disease, but once this has been excluded, it should be accepted as the ideal blood pressure in a healthy individual. In hypotension accompanied by symptoms, a primary cause should be sought. The psychic make-up of those hypopietic individuals who present symptoms with no demonstrable organic pathologic abnormalities should be carefully studied. Unless the underlying problem is a severe neurosis or psychosis, the patient need not be relegated to the care of the psychiatrist but can be managed by the internist or family physician familiar with the problem involved<sup>10</sup>. The low blood pressure encountered in the asthenic states will probably rise as the patient's general condition improves<sup>50</sup>, and usually the less said about the blood pressure the better, as the patient may consider the alleged deviation from normal as a grave indication. It is a mistake for the physician to offer these individuals an excuse for perpetuating their symptoms and accentuating their asthenic state: reassurance and sound psychotherapy are the most rewarding therapeutic procedures for alleviation of symptoms.

Constant supervision with attention to adequate nutrition, especially in those cases associated with anorexia nervosa and other cachetic states<sup>123</sup>, exercise and improvement of existing enteroptoses by abdominal binders and other methods<sup>136</sup> are beneficial. Drugs, such as benzedrine, epinephrin, ephedrine, paradrine, pitressin, ergot or other tonic drugs, are usually of little permanent value but occasionally offer temporary symptomatic relief, especially if they restore the subject's energy and confidence. Thyroid and commercial extracts of adrenal glands are probably of no assistance<sup>72</sup>.

The hypotension associated with various disease states may be approached by attempts to correct the altered physiologic conditions. In cases of diminished levels of sodium or chloride in the blood, administration of sodium chloride along with desoxycorticosterone may be warranted<sup>52,129,141</sup>. When hypoglycemia is encountered, glucose is indicated<sup>9</sup>. Necessity for treatment of anemic states is obvious, as is that of toxemias of infectious diseases by specific therapy.

Treatment of postural hypotension presents a special problem. MacLean<sup>79</sup> recommends having the patient sleep in a head-up position in an attempt to allow physiologic readaptation to the erect posture. Abdominal binders or leg binders<sup>65</sup>, various pressor drugs<sup>16,22,65</sup>, avoidance of exercise on warm days, and use of added salt and desoxycorticosterone<sup>52</sup> have all been suggested.

It cannot be overemphasized that management of hypotension should not be directed primarily at the blood pressure but rather at correcting the underlying cause, whether it be organic or functional. Elevation of the blood pressure without psychic stimulation has proved ineffective in the relief of symptoms<sup>39</sup>. Asymptomatic essential hypotension requires no treatment and should be regarded as the ideal pressure.

**Summary and Conclusions.** The literature concerned with hypotension has been reviewed and some of the important physiologic mechanisms responsible for its presence have been presented. An effort was made to correlate clinical findings with physiologic changes producing the symptoms and signs frequently associated with hypotensive states.

Though the terms "hypotonic" and "asthenic" have been freely used, it should be reiterated that any factor, psychic, physical, chemical, physiologic or pathologic, manifests its effect on the blood pressure only by its alteration of blood volume, peripheral resistance, cardiac output, size of the vascular bed or viscosity of the blood.

The fundamental clinical point to be gained by such a discussion is one which has previously been stressed many times: that hypotension is not a disease but rather is sometimes the manifestation of an altered physiologic state and sometimes the ideal level of blood pressure, suggesting freedom from cardiorenal disease and a promise of increased longevity.

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# NEUROLOGY AND PSYCHIATRY

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## NARCOLEPSY: BRIEF REVIEW AND REPORT OF CASES

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A conservative estimate<sup>7</sup> is that one-third of all patients who seek medical advice are victims of some disturbance of sleep. Although the majority of these patients suffer from insomnia, a sizable percentage complain of excessive drowsiness or sleepiness. This paper is concerned with a well-defined part of the latter category, narcolepsy, which compensates for its relative infrequency by its habit of invading and pervading most of the medical specialties with its bizarre symptomatology. The term "Narcolepsy" (Gr. *narkē*, sleep, and *lepsis*, a seizure)<sup>40</sup> was proposed by Gelineau in 1880 for what he considered "a rare neurosis characterized by an urgent need to sleep, sudden and of short duration, recurring at more or less close intervals"<sup>30</sup>. While thus naming the so-called "neurose rare" descriptively for the irresistible attacks of diurnal sleep, he also included in the clinical syndrome attacks of complete muscular tonelessness, either type of episode occurring spontaneously or precipitated by profound emotion. Emotionally induced loss of muscle tonus was named "cataplexy" (Gr. *kata*, down, and *plessein*, to strike)<sup>40</sup> in 1902<sup>58,16</sup>. Since Gelineau's memorable

paper "De la Narcolepsie"<sup>30</sup> was published, several hundred cases similar in symptomatology to those which he presented have appeared in the literature. Many excellent general reviews of the subject have been written<sup>43,16,58,9,61,67,15</sup>. Most authorities on the subject now look on narcolepsy as a symptom-complex rather than a distinctive disease entity<sup>34</sup>. Some reserve the diagnosis of narcolepsy for cases showing both the sudden attacks of diurnal sleep and cataplexy. This is the true or classical "Gelineau Syndrome". Others feel that in the present state of our knowledge, lines of differentiation should not be drawn too sharply<sup>16,17</sup>. As a result, cases of narcolepsy reported in the literature may be "with or without cataplexy", depending on the interpretation of the individual writer.

The symptom-complex of narcolepsy may consist of all or only a few of the following symptoms<sup>9,16</sup>: 1.) *Attacks of diurnal sleep*. This symptom is the single "sine qua non" for the diagnosis of narcolepsy, and is usually, but not necessarily, the most troublesome manifestation to the patient. Characteristically the attacks of sleep are abrupt in onset but may be preceded by a short period

of drowsiness which barely allows the patient time to retire to a safe or comfortable place for the oncoming attack. Patients so afflicted have fallen asleep while driving an automobile, while walking, talking, sitting at the dinner table, reading and so on. The situation in which the patient falls asleep is often one that is conducive to sleep in the normal individual. The actual sleep is clinically indistinguishable from normal sleep and can be terminated in the same manner with equal ease. A previous good night's rest or prolonged sufficiency of nocturnal sleep has no effect whatsoever on the urgency, frequency or length of subsequent sleep attacks. These episodes may occur from once or twice a week to as many as 200 daily. They last from a minute or two to an hour or so and leave the patient feeling keen and alert on awakening.

2.) *Cataplexy*<sup>20</sup>. Cataplexy usually consists of a sudden complete loss of tone of all the voluntary muscles of the body, beginning with the muscles of mastication. An overwhelming majority of these attacks are precipitated solely by jokes or humorous situations which evoke maximum sudden unexpected laughter in the patient. His jaw drops. His knees can no longer support his body, and, in a few seconds, he is like a mass of jelly lying on the ground, conscious but unable to talk or move. Within a minute or two he regains full use of his muscles and is normal in every respect. Less commonly cataplectic attacks may abruptly follow the emotional stress incidental to anger, fear, excitement, surprise, or weeping, or rarely may occur spontaneously, apparently unassociated with any specific emotion. Cataplexy usually has its onset at the same time as, or a few months later than, the sleep attacks. Cataplexy is very rarely a solitary symptom.

3.) *Sleep paralysis*<sup>11, 20</sup>. This symptom consists of a brief period of complete inability to move or talk

immediately preceding or following diurnal or nocturnal sleep. Consciousness is usually distressingly clear and the patient suffers acutely from fear of impending death or other disaster. The attack lasts from a minute or two to an hour or so and can usually be terminated at once by the simple touch of another individual. Sleep paralysis is a much less frequent concomitant of the narcoleptic symptom-complex than cataplexy, and occurred in only 8% of one series of 200 cases of narcolepsy<sup>9</sup>. Terrifying dreams often seem to precipitate those attacks of sleep paralysis which begin in the middle of the night or immediately after awakening in the morning.

4.) *Disturbed nocturnal sleep*. The nocturnal sleep of about 80% of narcoleptics is disturbed by insomnia, terrifying dreams, somnambulism, or somniloquism.

5.) *Hypnagogic hallucinations*. These consist of vivid stereotyped frightening dreams which are experienced in the half-awake state. They sometimes occur just prior to or during an attack of sleep paralysis and are rarely an isolated symptom. Hypnagogic hallucinations may persist for a short period into the partially or fully awake state and result in severe anguish and anxiety.

6.) *Paranoid psychotic state*<sup>9, 51, 51</sup>. Rarely, a chronic hallucinatory paranoid state seems to develop on the basis of the dream experience.

7.) *Gain in weight*<sup>15</sup>. In one large series of cases<sup>16</sup> almost half of the patients gave a history of a disproportionate gain in weight after the onset of narcolepsy. This tendency was more marked among women<sup>37</sup>.

8.) *Transient diplopia or transient ptosis*<sup>51</sup>. Although this symptom is not peculiar to narcoleptic patients it is occasionally seen prior to the sleep attacks or even independently of them.

9.) *Impairment or absence of libido*. This is found in 10 to 15% of the cases.

10.) *Headaches*. When present, headaches tend to appear immediately before attacks of sleep,

particularly if the latter are resisted, and are often completely relieved if the patient is allowed to sleep and awoken without interference.

Narcolepsy may be classified etiologically into the following groups: 1, *Idiopathic Narcolepsy*. Over one half of all cases of narcolepsy fall into this category and hence yield no evidence of organic disease. 2, *Symptomatic Narcolepsy*. This type follows tumors, inflammations and degenerative conditions involving the hypothalamus<sup>15,65</sup>. Sleep attacks alone, or in combination with cataplexy, are especially common after encephalitis<sup>58</sup>. Other diseases and conditions which are sometimes associated with the symptom-complex are: central nervous system syphilis<sup>50</sup>, head trauma<sup>38,58</sup>, cerebral arteriosclerosis, polycythemia vera<sup>61</sup>, diabetes, hyperinsulinism, acromegaly and multiple sclerosis. 3, *Cases associated with endocrine dyscrasias*. This is a presumptive explanation used in cases associated with obesity, alterations in metabolism and other symptoms suggestive of endocrine abnormalities. 4, *Cases complicating convulsive (epileptic) attacks*. 5, *Cases apparently of psychogenic origin*. This category includes those associated with hysteria<sup>70</sup>, and other neuroses, as well as the major psychoses<sup>18</sup>.

There is abundant clinical<sup>4,37,84</sup> as well as experimental evidence<sup>59</sup> that lesions of the hypothalamic nuclei and surrounding regions may cause hypersomnia and, or, narcolepsy<sup>53,73,87,18</sup>. Some authors have even postulated a "sleep" or "waking" center in this area<sup>59</sup>. The fact that man is able to fall asleep in a conscious or unconscious attempt to escape certain emotional difficulties, or to remain awake during emergency situations and periods of emotional stress, suggests that the higher cortical centers also play an important role in the regulation of sleep. The hypothalamus is in intimate connection,

by means of its pathways, with the cortex, thalamus, basal ganglia, and brain stem. Disturbances of sleep seem to result when the integration of this complicated mechanism is disrupted by destructive or irritative lesions or by emotional factors<sup>18</sup>. Hence, sleep is a function of the whole person<sup>23,22</sup>. Much scientific research has been done in an effort to determine if definite emotional constellations precipitate or aggravate the neurophysiological disturbances responsible for the manifestations of narcolepsy<sup>13,18,45,54,71</sup>. Every emotional situation is invariably associated with some physiological response such as sweating, palpitation, shortness of breath, pallor, blushing, blood pressure changes, erection of hair, sphincteric disturbances, laughing, weeping, sleeplessness or somnolence. Until recently medicine has paid little attention to the investigation of these processes as they were considered a part of normal life, common to everyone, and hence without ill effect. However, it is common knowledge now that persistent emotional disturbances may result in chronic bodily changes such as hypertension, peptic ulcer, asthma, mucous colitis and so on<sup>52</sup>. These physical responses apparently are mediated and controlled by the hypothalamus (a vegetative center) as well as by the cortex and possibly other subcortical structures<sup>18</sup>. The symptom-complex of narcolepsy has, in various patients, been found to be associated with repressed conflicts involving hostility<sup>27</sup>, guilt feelings, dependency needs, or various disturbed relationships between the patient and his environment<sup>13</sup>. The symptoms often appear to be neurotic defenses against anxiety, with symbolic significance<sup>45</sup>.

Many conditions must be considered in the differential diagnosis of idiopathic narcolepsy. First and foremost among them is idiopathic epilepsy. Gelineau expressed the opinion that



epilepsy and narcolepsy are unrelated. He said, "Peut-on voir la de l'épilepsie? Je ne le pense pas"<sup>30</sup>. That is still the view of most writers on the subject<sup>82</sup>. However, in most textbooks one finds narcolepsy discussed among the "convulsive disorders", "disorders of sleep", or perhaps even among "the epilepsies", primarily because of the difficulty in classifying this symptom-complex. The following are some of the similarities between narcolepsy and epilepsy: 1.) Psychoanalytic research indicates that in both conditions the symptoms inhibit, deflect, and prevent awareness and action which threatens to disrupt consciously accepted patterns of behavior<sup>13</sup>. This is best exemplified in cataplexy. 2.) A small percentage of patients are both epileptic and narcoleptic<sup>17 16,61</sup>. 3.) An occasional case of narcolepsy has a positive epileptic heredity<sup>61</sup>. 4.) Both are characterized by periodically recurring attacks which begin abruptly and are of "relatively short duration"<sup>16</sup>. The following are the even more striking differences between narcolepsy and epilepsy: 1.) Most of the authoritative evidence indicates that there is nothing in the character of the electrical discharges from the brain of the narcoleptic patient which would link them with the abnormal electrical discharges from the brain of the epileptic patient<sup>12,10,62 33</sup>. Most authorities agree that "the sleep records of narcoleptics are like those of normals except that the decline to a deep level of sleep is more rapid"<sup>10,22 58 21</sup>. The electroencephalogram is usually normal in idiopathic narcolepsy during "the awake period"<sup>13</sup>. Symptomatic narcolepsy is much more likely to show other electroencephalographic abnormalities. 2.) Mental deterioration is a frequent sequel to epilepsy characterized by frequent seizures, and the seizures vary markedly in frequency throughout the life of the patient<sup>70 71</sup>. Patients with idiopathic narcolepsy, on

the other hand, suffer from no intellectual impairment, regardless of the frequency of their attacks; and, in untreated cases, the number and severity of the attacks are much less subject to amelioration or exacerbation<sup>16</sup>. 3.) Narcoleptic attacks are not accompanied by convulsive movements, biting of the tongue or cheeks, or loss of bladder or bowel control. After a sleep or cataplectic attack the patient is usually alert<sup>30</sup>. In cataplexy there is usually conscious awareness of environmental sounds and events in spite of the relative or absolute muscular immobility and inability to speak. The fact that cataplexy is emotionally precipitated is usually obvious to the most untrained observers and acquaintances of the patient. 4.) The commonly used anti-convulsant drugs<sup>42</sup> are completely ineffective in relieving narcoleptic attacks. 5.) The diurnal sleep attacks of narcolepsy (except for their abrupt onset) are similar in every respect to normal physiological sleep, and can be terminated with equal facility.

The differentiation of idiopathic narcolepsy from narcolepsy secondary to organic disease, endocrine dyscrasias and psychogenic factors will naturally depend on the individual physician's proficiency in the diagnosis of those conditions. Other diseases and conditions which must be differentiated are: coma from any cause, hookworm disease, trypanosomiasis, the drowsiness of fatigue, the lethargy of convalescence from febrile illnesses, the fatigue common to chronic wasting diseases, the somnolence of asphyxia, the drowsiness or somnolence of over-sedation, and acute alcoholism<sup>64</sup>. Probably the most important consideration is for doctors to keep in mind the possibility of narcolepsy in their differential diagnoses. Clinical guesses frequently made on narcoleptics have included over-drinking of milk, neurocirculatory asthenia.

laziness, and disbelief in the patient's statement<sup>35</sup>.

There are several interesting military aspects of narcolepsy. As a "disturbance of consciousness", it is a cause for rejection for military service<sup>2</sup>. Since idiopathic narcolepsy occurs several times more often in males than in females, and usually has its onset before the age of 25, it is apparent why many cases of this symptom-complex have appeared among military personnel<sup>26,50</sup>. Soldiers on guard duty who fall asleep while in the performance of this important function are usually subjected to disciplinary action<sup>34,67</sup>. (This has been considered a major military offense by all armies down through the ages.) In some cases, however, a defense on medical grounds is appropriate and just. During World War II, one psychiatrist<sup>49</sup> reported that "Of 25 soldiers discovered asleep on post as sentinels, they were divided into the following 3 groups: *a*, Four men were rebellious psychopaths who fell asleep intentionally. *b*, Nineteen men were, in the main, good soldiers, who fell asleep because they more or less carelessly had failed to get enough sleep before going on post. *c*, Two men had narcolepsy." A War Department publication on the subject of military training<sup>83</sup> advises that "morning hours should be used for training requiring the greatest mental concentration. Afternoons are suited to subjects requiring action and movement". Interestingly enough, narcoleptics have a tendency to develop sleep attacks during the same monotonous or post-prandial periods which ordinarily cause drowsiness in the normal individual. Then, too, the narcoleptic can often dispel drowsiness, at least temporarily, by physical exertion. Since narcoleptic symptoms are bizarre, the victim of such a condition in the military service is often at first called "lazy" or "Rip Van Winkle", reduced to the grade of private for falling asleep

during lectures and demonstrations, and given more and more menial assignments. However, since even top-sergeants have a limit to their endurance, the narcoleptic eventually is sent to the hospital. There is certainly some similarity between cataplexy and the condition of some combat soldiers who become "paralyzed" by fear. "This fear paralysis is also seen in animals, as when a small animal is unable to escape from an approaching snake"<sup>77</sup>. Another writer<sup>86</sup> stated that "It must have meant safety to the animal to lie motionless as though dead. From this aspect at least, the phenomena of the affective cataplectic fit fall into line with reactions phylogenetically ancient, and are capable of psychological and teleological explanation. It would appear that the mechanism once utilized by fear to produce motionlessness can also be activated by an emotion of opposite quality." The most decorated American soldier of World War II, in his realistic book, "To Hell and Back"<sup>57</sup>, tells of the unexpected appearance of two German soldiers at the front during the Italian campaign. Of the incident he said, "As we prepare to leave, two straw-laden figures round the stack. For an instant, the four of us stand stupidly sharing a mutual paralysis of surprise. Then, still clutching our straw, we take off." Another author<sup>49</sup> stated that "Soldiers brought up to the front line have fallen asleep under their first bombardment. The experiments of nature duplicate Pavlov's on conditioned inhibition. When a man perceives a peril from which he wants to escape, but is deterred by some other circumstance such as the wish to appear brave, he is being acted on by an 'inhibitory combination' of stimuli: excitations which under simpler conditions would be given free rein are now checked by an inhibitory process. Narcoleptics betray an undue susceptibility to inhibition." Several cases of sleep paralysis are

reported to have occurred in "returned Air Force personnel suffering from combat fatigue. The condition occurred singly, not in association with cataplexy, narcolepsy, or somnambulism. Superficial analysis led to the impression that sleep paralysis is, in all probability, related to a state of confusion as to emotion and intention, with resulting indecisiveness"<sup>80</sup>. Another writer stated that "In sleep paralysis sleep does not normally spread rapidly and diffusely through the nervous system, but the motor and postural centers fall asleep before the mind, or in awakening the mind awakens before the body; in somnambulism the reverse occurs—the motor and postural centers are active while the mind is asleep"<sup>8</sup>. It has also been reported<sup>47</sup> that hypnagogic hallucinations are at times found in the early stages of war neuroses.

Amphetamine (benzedrine) sulfate and ephedrine sulfate are the drugs of choice for the treatment of narcolepsy. A tremendously large literature has accumulated on the effectiveness and action of each. Most authorities feel that benzedrine is the more effective drug<sup>1,7,17,22,58,62,67,75</sup>. Several writers have agreed that ephedrine is often more effective in controlling the attacks of cataplexy than the attacks of sleep<sup>7,58</sup>. One report<sup>20</sup> stated that 6 patients obtained symptomatic relief from the sleep attacks as well as the cataplectic attacks by the combined oral administration of potassium chloride (10 grains after each meal) and benzedrine sulfate (10 grains, 2 or 3 times daily). Apparently, potassium chloride was considered effective against the cataplectic component (and in one case also against the sleep paralysis), and benzedrine against the sleep component. One writer states that "Alternate doses of amphetamine and ephedrine may be efficacious in some cases"<sup>1</sup>. Benzedrine has been advocated as an addition to the usual

anticonvulsants in cases of epilepsy complicated by narcolepsy<sup>16</sup>. Dexedrine sulfate, the dextrorotatory isomer of benzedrine sulfate, is also reported to be effective in narcolepsy but the reports are few in number<sup>18,41</sup>. A few but unimpressive number of cases of narcolepsy have been benefited by oral thyroid extract<sup>16</sup>. Other drugs which have been tried, largely with little or no benefit, are caffeine, strychnine, irradiated ergosterol, theelin, and pituitary extracts<sup>20</sup>. Benzedrine sulfate was first introduced in America for the treatment of narcolepsy in 1935<sup>64,74</sup>. As the result of a great deal of research<sup>28,39,44,58,14</sup> we know that the main contraindications to benzedrine are hypertension, coronary disease, manic excitement, and severe exhaustion<sup>75</sup>. There is also good evidence that serious addiction or habit formation do not occur with benzedrine, even after its daily ingestion for many months to several years<sup>5,74</sup>. Symptoms of overdosage of or individual intolerance to benzedrine include hyperexcitability, restlessness, dilated pupils, inability to relax, dizziness, nausea, vomiting, and insomnia<sup>41,64,75,82</sup>. The (unlikely) possibility of benzedrine precipitating a psychosis is raised by one author<sup>85</sup>. A suicide<sup>31</sup> and an accidental fatal poisoning with benzedrine have also been reported. The average oral dosage of benzedrine for the treatment of narcolepsy in adults is 10 mg. 3 times daily, the first 2 doses before breakfast and lunch, and the last dose not later than 3:30 P.M. in order not to interfere with natural nocturnal sleep<sup>64,67,80,87</sup>. The exact dosage will depend on the age of the patient and the severity of the disease. As there is individual variation in response to benzedrine, it is best to start with a total daily dose of 10 mg. and gradually increase it until the optimal effect is obtained. When using ephedrine sulfate, the plan of treatment is to prescribe the oral administration

"of a capsule containing 25 mg. of ephedrine sulfate before breakfast, before lunch and at 4:30 P. M. If the patient is not entirely relieved, the morning and noon doses are increased to 50 mg., but the late afternoon dose is kept as low as possible, and in some instances is omitted, in order to avoid disturbing nocturnal sleep. A few patients have taken as much as 75 mg., while others have obtained relief from 16 mg."<sup>16</sup> L. E. Daniels (at present Professor of Neurology at Colorado University School of Medicine) and an associate were the co-discoverers of the use of ephedrine in narcolepsy<sup>16</sup>. The symptoms of overdosage of ephedrine are tachycardia, tremulousness, hyperexcitability, and insomnia<sup>75</sup>. However, severe reactions to ephedrine are uncommon<sup>72</sup>. As there is increasing evidence that the psychogenic element is large in some cases of narcolepsy, many cases of the treatment of this condition by psychotherapy have been reported<sup>15,34,55,80</sup>, often with marked amelioration of the patient's symptoms or an actual cure<sup>48,61,76,78,18</sup>. F. G. Ebaugh<sup>22</sup>, in his training of students and psychiatric resident physicians, has always emphasized the importance of treating the patient as a whole rather than as a system of isolated organs or emotions. The handling of cases of narcolepsy exemplifies the necessity of such a plural approach. The following cases of narcolepsy were diagnosed and treated in one of the hospitals or clinics of Colorado Medical Center:

CASE 1. A. L. M., a 13-year-old white boy, was first seen in the Pediatric Neurology Clinic of Colorado General Hospital in July, 1946, complaining of frequent irresistible attacks of diurnal sleep and "falling down spells" of 2 months duration. The "falling down spells" were always preceded by laughter at some humorous situation and caused the patient to fall to the ground and remain there for a minute or two. He was always conscious while on the ground but could neither talk nor move. For several weeks after the onset of his illness he suffered from

"dreams of terrible things in which humans took part. He was restless at night and tore up his bed and bed clothes and talked in his sleep for a while." The following examinations and tests were negative: General physical and neurological examination, electroencephalogram (patient awake), spinal fluid, Roentgen-ray examinations of the chest and skull, basal metabolism (-9), blood counts and hemoglobin, blood sugar and nonprotein nitrogen, blood Wassermann and Eagle Flocculation Test. There was no history of head trauma or disease suggestive of encephalitis. Benzedrine sulfate (beginning with 2.5 mg. B. I. D. and gradually increased to 15 mg. B. I. D.) was not very effective in reducing the sleep or cataplectic attacks. Oral ephedrine sulfate ( $\frac{1}{2}$  gr. T. I. D.) was more effective but not entirely satisfactory. Inquiry into the home situation revealed that the patient's symptoms began one week following the remarriage of his father. The boy openly resented this newcomer to his father's household. The stepmother considered the boy "stubborn and undisciplined" and felt it her duty to "train him right." The neurologist, the pediatrician and the psychiatrist were equally convinced that the constant "tug of war" between the boy and his stepmother would have to be resolved before treatment with any medicine could be effective. Psychotherapy was advised but the stepmother was extremely defensive, on the grounds that "What he needs is to get away from the hospital atmosphere. I'll handle this situation."

This is a typical case of idiopathic narcolepsy with a probable emotional component as the precipitating or aggravating factor. We know that the emotions affect the symptomatology of organic as well as of functional diseases. For example, the tremors of Parkinson's Disease are markedly increased by anxiety.

CASE 2. J. W. S., a 12-year-old white boy, was first seen in the Pediatric Neurology Clinic of Colorado General Hospital in July, 1946, with the following complaints: "I have had sleeping spells for a year now, 3 or 4 times a day. They come on usually when I ain't got nothing to do. The other kids think it is funny when I fall asleep in school, but I don't think it is funny. My teacher makes me stand up to keep me awake. Walking will keep me awake. I sleep for a minute or two up to an hour or so. I don't sleep well at night since these sleeping spells

began but never dream. About two weeks after the sleeping spells began I was running home after a drum lesson. It was raining and I wanted to get home before I got too wet. I slowed down in the middle of a street and then just collapsed. I didn't know what had happened but got up right away. I hadn't been laughing or anything. The next day at the dinner table Dad told an awful funny joke. My whole head collapsed on my chest and my jaw opened. I couldn't talk a bit. My eyes were open and I could see and hear everything. It lasted half a minute out of a chair in those spells. I have only skinned my knees a couple of times from falling down. I fall down any time of the day when I laugh hard at something funny. First my jaw opens wide and then my legs get weak and then, bam, I drop to the ground in a heap. It all takes only a few seconds. My eyes are shut while I'm falling but as soon as I hit the ground I can open them. I can see and hear everything that is going on during a spell. In school I put my handkerchief in my mouth to keep from laughing or put my hands over my ears to keep from hearing the jokes. It usually works. When I'm swimming and get to laughing my jaw drops down and I swallow a lot of water. So I turn over on my back and float until my jaw gets strong again. The other night I was just talking to some guys and I wasn't laughing or thinking of anything funny, just talking natural. All of a sudden my knees and jaw got weak. I asked the fellows real fast to hold me up, but they thought I had a disease that was catching and took off and never came back. It was at night and I hit the ground. I knew what was going on and could even move my arms and legs a little but not enough to get up. After a minute I could sit up. In another half minute I was as strong as ever." He denied attacks of sleep paralysis, somnambulism and somnolism. There was no history of head trauma or encephalitis. The only childhood diseases which he had had were chickenpox at 6 years and measles at 7 years, both mild and uncomplicated. Physical and neurological examinations were and still are negative except for eczema of the face. At present, he is 65 inches tall and weighs 130 pounds. He is well proportioned and his body configuration shows no evidence of endocrine disorder. The following examinations were negative: Repeated urinalyses, blood counts and hemoglobin, blood sugar and nonprotein nitrogen, blood Wassermann, spinal fluid, Roentgen-ray examinations of the chest and skull. The electroencephalographic report of

December, 1946, stated that "The sudden appearance of short bursts of sleep waves is like that frequently seen in narcolepsy." He was started on amphetamine (benzedrine) sulfate, 2.5 mg. T. I. D. (after breakfast, lunch, and at 3:00 P. M.). This dosage was gradually increased to 15 mg. T. I. D. and was sufficient to prevent 90% of both the sleep and cataplectic attacks.

His past history revealed that he has suffered from severe eczema since the age of 3 months and that he has been treated for this condition almost continuously since then. Other children were afraid of "picking up his skin disease," but in general accepted him until he developed narcolepsy. Within a year after the sleep attacks appeared, the patient resigned from the Boy Scouts, the Y. M. C. A., and the school band as he felt that all of his friends had deserted him. He has no affection for his father, who divorced his mother in 1939, and in fact is very hostile toward him "for the bad beatings he used to give me over nothing." His mother has had to work outside the home since 1941 in order to support her four children. "The children have had to raise themselves since then." Within a few months after the onset of narcolepsy the patient developed a marked change in personality. He was placed on probation by the Juvenile Court for stealing money from his father and for collecting money from other boys' paper routes. He became increasingly irritable and threw knives and ice picks at his older brother. He played truant from school at frequent intervals and ran away from home several times. Because of these difficulties both the patient and his mother were treated at the Mental Hygiene Outpatient Clinic of Colorado Psychopathic Hospital at regular weekly periods, beginning in February, 1947. The patient was treated for 5 months, with moderate improvement in his behavior difficulties. However, the mother stopped her own treatment after a few interviews "because this is my son's problem, not mine, and besides I have to work every day". Brief psychological testing more than 2 years ago revealed "A full I. Q. of 74 (classification, borderline defective). The Brown Personality Inventory for Children shows a poor home adjustment, insecurity, irritability and undue concern over his physical well-being."

One year ago, the patient quit school because of poor grades. Since then he has worked at various odd jobs for a few weeks at a time. He talks from the corner of his mouth with the appearance and accent of a "Dead End Kid." Psychological tests (The Rorschach and Thematic Apperception Tests), interpreted by a clinical psychologist<sup>23</sup> of

Colorado Psychopathic Hospital's Department of Psychology, revealed the following: "The diagnostic impression is a neurotic depression. In his stories the mother is a hostile rejecting figure. He tends to solve problems by evading them. He is resigned to his father's hostility and reacts to it passively. He is afraid to strike back. It is interesting that in some of his stories he evades striking back at men by going to sleep."

This also is a typical case of idiopathic narcolepsy. Unfortunately it was engrafted on a personality already crippled by the frustrations of a life-long disfiguring eczema and borderline mental deficiency. In spite of it, however, this patient can probably be kept from being a menace to society, by medical and psychotherapeutic measures available to the general practitioner<sup>25</sup>.

CASE 3. J. D. E., a 14-year-old white boy, was first seen in the Pediatric Neurology Clinic of Colorado General Hospital in February, 1949, complaining of "headaches, sleeping and falling spells". His mother said: "Since June, 1948, he has fallen asleep about 6 times every day, usually when he sits down and has nothing much to do. He closes his eyes and is asleep just like that (snapping her fingers). He never falls asleep outside when he is doing the chores, only when he comes inside. He has complained of rather sharp headaches also since June, 1948, and nothing but sleep will stop them, not even aspirin. He never has headaches at night. I usually have to shake him a little and call him to wake up. He wakes up in about a minute, and is usually cranky if I wake him up before he has slept about 20 minutes. He often falls asleep while he is reading. It looks like ordinary sleep to me. He has even gone to sleep while he is sitting at the supper table, but never during an interesting discussion. He goes to sleep instantly. Five months after his sleeping attacks began, his falling attacks started. Whenever he hears a funny joke and laughs out real hard his arms and legs just kinda dangle and he falls to the ground. His knees just give away and it is a minute or two before he can get up. While he is there on the ground, his eyes are open and his jaw is dropped. He would make kind of a funny noise with his throat like he was still trying to laugh but couldn't get it all out. He never gets unconscious or soils his clothes. He never twitches or jerks during these spells and

always hears the end of the joke that he was listening to. He never goes to sleep after the spells." The patient said, "The headaches are sharp and just on one side, from the right side of my nose to the right middle part of my head, not often on the left side. I have the headache every day, sometimes in the morning and sometimes in the afternoon. It is not usually severe. It stays 10 or 15 minutes and sleeping stops it mostly. Even with aspirin I have to sleep to stop it. I feel sleepy for a while before I fall asleep. Getting up and running is the only way I know to stop the sleep, or if somebody teases me real strong. If I stay out of breath I won't sleep but fall asleep when I stop breathing hard. If I just trot I'm still sleepy but if I run with all my might I'm not sleepy. I stay asleep 1 to 1½ hours and feel fine when I wake up. I never sleep after laughing real hard. I never go to sleep while I'm walking. I usually fall asleep when I ain't got nothing to do or when I'm not interested. At school it is usually in the afternoon when I fall asleep as I don't like the teacher. I get mad when anybody wakes me up. Last summer for a while I used to wake up at night scared and in a cold sweat as I would dream of monsters or snake pits. But now when I dream it is about going to school or something like that, not scary. I never walk or talk in my sleep. I sleep 8 to 10 hours every night, but sleeping more does not keep me from getting sleepy in the day. The falling down spells are much more trouble to me than the sleeping. I start to laugh, get out a few laughs and then lose control of my muscles all over and I just fall down. I stay down for a minute or so and know everything that is going on around me. I can hear them talk and can see them walking around. Once in a while, though, while I'm down my mind isn't real clear and I get clouds over my eyes and I can't see real well. When I get control of my muscles the cloud goes away from my eyes and I'm all right. Shaking me or talking to me brings me out of it. Mom always says, 'Stop that'. I fall whenever I hear a real funny joke and sometimes I feel weak after it and have to sit down for a while, but not most of the time. Laughing is the only thing that makes me fall but when I cry real hard when I'm mad, my knees get weak for a few minutes. I also get weak knees when I get mad at our calf for running away from me, but I don't fall. That calf sure makes me mad when he runs off. When I laugh hard at school, when I'm sitting down, my arms drop to my sides and my head hits the desk with a bang and that snaps me out of it and I'm all right. The same thing happens if I fall asleep in

my seat. I fall down from laughing any number of times a day, depending on how many times I laugh. At school, the kids sometimes try to make me laugh to see me fall. They think it is funny. To keep from falling down I try not to laugh and put my chin down on my chest. If I push my chin down on my chest and shake my head I just fall down on my knees and then get right back up. I have never hurt myself falling down. Sometimes I can't concentrate lately, for example when a kid makes a noise. My memory might be a little poor as I forget things easily that I have done, especially in History or in English. I have to get up every night to urinate since the sleepiness began." He denied symptoms of sleep paralysis.

Physical examination was essentially negative. He is 65 inches tall and weighs 143 pounds. He has gained 15 or 20 pounds of weight during the past year. He has adult type genitalia and a moderate amount of public and axillary hair. He is heavily muscled and well proportioned. He appears at least 2 years older than his stated age. He is left handed. Mental status examination revealed a sober-faced boy of 14 years who neither smiled nor laughed. He seemed to be of about average intelligence and carried on a normal conversation. His words and accents smacked of a farming community. There was no evidence of psychosis. Psychological tests<sup>63</sup> revealed "a Full Scale I. Q. of 92, a Verbal Scale I. Q. of 96, and a Performance Scale I. Q. of 91. The classification is average. The subtest scatter and variability of performance of the Wechsler-Bellevue suggest a neurotic impairment of functioning rather than organicity. The Rorschach suggests an obsessive-compulsive neurosis. His stories, in the Thematic Apperception Test, describe an overprotective mother on whom the son is extremely dependent. He feels insecure and fears rejection by the mother. He is very hostile to his father, but is afraid to express it for fear of retaliation. If he expressed hostility toward his mother it would threaten his dependency gratifications. The many death stories suggest that he tends to introject his hostility. The stories dealing with sleep, or rest, or unconsciousness, suggest that his narcolepsy may be a useful mechanism for avoiding expression of hostility." The following examinations were negative: Urinalyses, blood counts and hemoglobin, blood Wassermann, blood sugar and nonprotein nitrogen, spinal fluid, Roentgen-ray examinations of the chest and skull, and basal metabolism (-7). The report on the electro-encephalogram was as follows<sup>10</sup>: "Most of the record is a sleep record. This examination presents evidence of a

severe diffuse paroxysmal cortical disturbance with the principle disorder in the anterior portion of the cortex."

Birth and developmental history were normal. He had chickenpox at 1 year, mumps and measles at 4, and whooping cough at 6, all mild and without complications. There was no history of high fever, coma or somnolence prior to the present illness. However, according to his mother, when he was 2½ years old he fell backward off a bed and hit his head on the floor. He was not rendered unconscious but "complained of headache across his forehead after that until he was 6 or 7 years old". There were no neuropathic traits. Psychosexual development was normal. He has one brother, 20 years of age, and 2 sisters, one of whom is 16 and the other 10 years of age. His father and mother were divorced 3 years ago. Since then the mother and children have been supported by the County Welfare.

Treatment consisted initially of oral ephedrine sulfate (gr. ⅓ before breakfast and lunch). Two weeks later another gr. ⅓ capsule was added to the daily dosage, at 4:30 P. M. The cataplectic attacks were almost completely abolished, and the sleep attacks were reduced to about one daily, always after the evening meal. Perhaps at a later date he will be tried on benzedrine sulfate. However, ephedrine sulfate has almost abolished his chief complaint, the cataplectic component.

This case also presents the classical symptoms of idiopathic narcolepsy, but the history of head trauma<sup>34</sup> and the abnormal electroencephalogram findings cast some doubt on the "idiopathic" etiology. However, the question is of purely academic interest as the treatment is the same in either case<sup>17</sup>.

CASE 4. L. R. K., a 16-year-old white boy, was admitted to Colorado General Hospital in June, 1947, because of sleep attacks and "falling spells" of one year's duration. Both types of attacks started about one month following the onset of an exceptionally severe case of acute infectious hepatitis. His sleep attacks occurred 5 to 6 times daily and were typical in every way. The cataplectic attacks also were typical and followed immediately "whenever he got excited or laughed real hard about something". General physical and neurological examinations, as well as the following, were entirely negative: Urinalyses, blood counts and hemoglobin, blood sugar and nonprotein nitrogen, blood Wassermann,

spinal fluid, and Roentgen-ray examinations of the chest and skull. The initial dosage of amphetamine (benzedrine) sulfate of 5 mg. after breakfast and after lunch was increased to 10 mg. twice daily. This latter dosage abolished the attacks of tonelessness following laughter and diminished the sleep attacks to about one daily. A recent follow-up report shows that the patient is doing very well in high school and will graduate this year. He is a star member of his school football team.

This is apparently a case of symptomatic narcolepsy, the result of an encephalitis (or localized degenerative process in the hypothalamus<sup>60</sup>) complicating acute infectious hepatitis<sup>68</sup>. This type of narcolepsy has been reported previously<sup>16</sup>. Involvement of both liver and brain, in acute and chronic hepatic disease, is of common occurrence. Such diseases as Wilson's Disease (hepatolenticular degeneration) and kernicterus are well known examples<sup>3</sup>.

CASE 5. R. G., a 26-year-old single white male, was admitted to Colorado Psychopathic Hospital in July, 1942. The patient, the son of Mexican parents, gave the following account: "In 1941 I had a quarrel with my girl and her aunt, and her aunt didn't approve of me. I was disgusted and joined the army. About that same time I started getting sleeping and drop spells. When I'd go on marches with my unit I would fall asleep during the short rest periods—also during class periods. I told an officer that I could carry on normally the rest of the day if I could only take a few naps. He got mad and had another soldier slap me whenever I got sleepy. That made me awful mad. They finally sent me to the hospital and I was discharged as having narcolepsy, after being in the army for only 3 months." His parents said, "These sleeping spells last 15 to 60 minutes and occur several times a day, mainly when he is doing nothing in particular but sometimes when he is at the dinner table or while he is talking to someone. The drop spells usually follow temper tantrums when he is mad about something. He just falls down and can't move or talk for a minute or two. He loses control of his jaw and tongue. For years he has been hard to get along with, and argues, and always thinks that he knows everything. For the past year he talks in his sleep at night and has wild imaginations. For years he had the idea that his family doesn't like him."

His past history revealed that the only childhood disease he had had was a mild case of measles at 13 years of age. There was nothing to suggest encephalitis. He gave no history of head trauma. He completed almost 2 years of college, majoring in education. He quit college at the age of 20 because of the development of multiple somatic complaints. No organic disease was ever discovered to account for the complaints. From then until joining the army he was an ineffective helper on his father's farm. After discharge from the army he continued working on his father's farm, and was a constant source of annoyance because of his belligerent and superior attitude. The father is described as a domineering patriarchal type of man who insisted on governing his family with iron discipline.

Mental status examination revealed a seclusive individual with many somatic complaints. He had several sleep attacks daily while in the hospital but no cataplectic attacks. He was irritable and demanding, and believed that everybody was against him and talked about him. He admitted terrifying auditory and visual "hallucinations" at night which took the form of snakes and dragons. His I. Q. was 102. Physical examination was entirely negative. The following examinations were also negative: Urinalysis, blood counts and hemoglobin, spinal fluid, blood sugar and nonprotein nitrogen, blood Wassermann, blood bromide, Roentgen-ray examinations of the skull and gastrointestinal tract, electrocardiogram, basal metabolic rate ( $-13$ ). On the morning of his 9th hospital day he was started on 5 mg. of benzedrine sulfate orally and was to have received the same dose in the afternoon. However, that afternoon the patient's father signed him out against medical advice before the effectiveness or optimum dosage of the benzedrine sulfate could be determined. The final diagnosis was "Paranoid Schizophrenia with Narcolepsy". Follow-up study revealed that the patient's narcolepsy is well under control with small doses of benzedrine sulfate. However, he is still an ambulatory paranoid schizophrenic who is making a borderline adjustment to society.

The relationship of some cases of narcolepsy and paranoid psychoses has been discussed in the literature<sup>9,16,51,61</sup>. However, the exact relationship is still obscure<sup>17</sup>.

CASE 6. W. C., a 19-year-old single white male, was admitted to Colorado Psychopathic Hospital in June, 1928, with the primary complaint of frequent diurnal attacks of irresistible



sleep. The sleep attacks had been present since he recovered from a severe case of "influenza" in September, 1925. Cataplectic attacks (which were precipitated by sudden laughter), insomnia, nocturnal restlessness and terrifying nightmares had developed a few months after the onset of the "sleeping spells" and had persisted to the time of his admission to the hospital. Mental status examination was negative except for the patient's "marked tendency to fall asleep during the day". Physical examination was negative except for a central type of facial weakness on the left side. The following examinations were also negative: Urinalysis, blood counts and hemoglobin, blood Wassermann, spinal fluid, Roentgen-ray examinations of the skull, and basal metabolism (+1). The diagnosis was "Chronic Encephalitis with Narcolepsy". At that time, 1928, there was no known effective treatment for this type of narcolepsy. However, in 1930, immediately after ephedrine was proven to be of benefit, Dr. F. G. Ebaugh administered ephedrine sulfate to the patient in oral dosages of gr.  $\frac{3}{4}$  three times a day. Marked symptomatic improvement resulted. One year later he was attending college and was on the school football team. An attempt was made to contact this patient for a follow-up study, but he had moved out of the state and could not be located.

This case is representative of that type of symptomatic narcolepsy which is secondary to chronic encephalitis<sup>15</sup>. Many such cases have been reported in the literature<sup>61,77</sup>. In general the prognosis in this type of narcolepsy is considered better than in any other type<sup>16</sup>. The behavior disorders<sup>36,54</sup> as well as the narcoleptic attacks<sup>29,58,33</sup> which may appear as postencephalitic residuals often respond favorably to psychotherapy<sup>18,54</sup>.

**Summary. 1.** A review of the subject of narcolepsy is presented. This included its historical background, symptomatology, etiology, pathology, psychopathology, differential diagnosis, electroencephalographic characteristics, military aspects, and treatment.

**2.** Six cases of narcolepsy are presented. The first two cases are definitely

of the idiopathic type. The third case is either idiopathic or secondary to head trauma. The fourth case was apparently secondary to a severe case of acute infectious hepatitis. The fifth case was associated with a schizophrenic psychosis. The sixth case was encephalitic in origin.

**3.** The second and third cases give the patients' own descriptions of their narcoleptic attacks. In addition, the third case gives a mother's impression of her son's illness. These were included in order to acquaint the reader with the detailed clinical picture of typical cases of narcolepsy.

**4.** The second and third cases, in addition, were given psychological tests in order to contribute to the present knowledge of the emotional conflicts and personality patterns of narcoleptic patients. There is a definite suggestion in both cases that the narcoleptic attacks were utilized to evade unpleasant emotional conflicts.

**5.** Psychotherapy at the specialty level was offered to the first two patients, with acceptance and satisfactory results in the second case.

**6.** It should be emphasized that psychotherapy in many cases of narcolepsy is not beyond the scope of the general practitioner, internist or pediatrician handling the patient<sup>85</sup>. The methods and concepts are clear<sup>24,25</sup>, and the amount of human suffering that can be reduced by their proper utilization is great.

**7.** Although amphetamine (benzedrine) sulfate is usually the more effective drug in the treatment of narcolepsy, its older sister, ephedrine sulfate, is at times more effective, and should not be forgotten in the mad rush for something "new and different."

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## PHYSIOLOGY

PROCEEDINGS OF

### The Physiological Society of Philadelphia

SESSION OF MAY 17, 1949

**Production of Convulsions in Rats by Exposure to Ultra High Frequency Electrical Currents (Radar).** G. M. AUSTIN, M.D., and S. HORVATH, Ph.D. (Depts. of Neurosurgery and Physical Med., and Grad. Sch. Med., Univ. of Penna.). Previous experimental work on the effects of radar pulsations on man and animals, indicated that no harmful effects resulted. This paper deals with the effects of continuous radar pulsations at short distances on a group of 47 rats. The dorsal surface of the head was exposed to a wave length of 12.2 cm. for varying periods of time. Sixteen rats were exposed to a 60 watt energy output at 2.5 cm. distance, and 25 rats exposed to a 90 watt output at zero distance from the skull. In 6 rats the director was focused over the spinal cord. Those rats exposed to a 60 watt output showed clonic type convulsions in a mean time of 2.8 minutes. These rats had an average increase in rectal temperature of  $4.2^{\circ}$  F. Those exposed to 90 watt output convulsed in a mean time of 1.2 minutes. There was no generalized hyperthermia in these rats. Brain temperature measured in 8 rats showed an average temperature of  $110.4^{\circ}$  F. immediately after onset of convulsions, although in those exposed to 90 watts there was no associated increase in rectal or thigh muscle temperature.

No pathological changes were found in any of the brains of sacrificed rats severe enough to explain the convulsions. Mild pyknosis, in the Purkinje cells of the cerebellum, in the Pyramidal layer of Ammon's Horn, and in the

third layer of the cerebral cortex were the only findings outside of moderate congestion. In those animals with the director placed over the spinal cord, no convulsions were noted, although rectal temperatures occasionally rose as high as  $112^{\circ}$  F.

It is concluded that a specific rise in the temperature of the brain itself is the most important factor in these convulsions, and a generalized hyperthermia has no bearing on the onset of convulsive activity.

**Respiratory and Circulatory Reflexes From the Heart and Lungs Initiated by the Veratrum Alkaloids.** DOMINGO M. AVIADO, JR., M.D., and ROBERT G. PONTIUS, M.D. (Lab. of Pharmacol., Univ. of Penna.). Preparatory to the study of respiratory and circulatory reflexes arising from the heart and lungs, the site of action of one of the veratrum alkaloids was investigated. Intravenous injection of the alkaloid has been repeatedly shown to cause reflex apnea, bradycardia and hypotension by acting on receptors in the chest. Almost all previous attempts at localization of the receptors were on open-chest preparations and the observations were on the circulatory reflexes. Catheterization of the different parts of the cardio-pulmonary circulation of anesthetized dogs (morphine and chloroform) has enabled the localization of the receptors responsible for the reflex apnea.

Injection of veratridine in dose of  $1\mu\text{gm.}$  per kg. into the left or right pulmonary artery or into the artery far

out in the substance of the lung was followed by an immediate apnea and hypotension and bradycardia about 5 seconds later. The apnea is due to the drug action on pulmonary receptors because cold block of the ipsilateral cervical vago-sympathetic trunk eliminated the reflex apnea without noticeably changing the circulatory response. Subsequent warming was followed by the return of the apneic response to the drug. The specific nature of the respiratory effect from pulmonary receptors is noticeable by inhalation into the lower respiratory tract of concentrated veratridine solution in mist form. The cardiac receptors were stimulated as long as a sufficient concentration of the drug could reach the coronary artery. Although their response was predominantly circulatory, they slightly inhibit respiration.

There are receptors in the carotid region exclusive of the carotid sinus pressoreceptors, that respond to veratridine with hyperpnea, bradycardia and hypotension. The chemoreceptors in the carotid body sensitive to cyanide can explain the hyperpnea but not the circulatory effects. The hypotension which is common to the carotid and cardiac receptors was shown by femoral blood flow measurements to be accompanied by vasodilatation.

The reflexes initiated from the heart and lungs by veratrum are different from the previously reported cardiac and pulmonary reflexes. They await further investigation for their physiological significance.

#### Isotopic Studies of the Biosynthesis of Nucleic Acid Components. II. Allantoin. JEROME D. VALENTINE, M.D., D. WRIGHT WILSON, Ph.D., and SAMUEL GURIN, Ph.D. (Dept. of Physiological Chemistry, Sch. Med., Univ. of Penna.).

It has been demonstrated by Buchanan, Sonne and Delluva (J. Biol. Chem., 173, 81, 1948.) that glycine,

acetic acid, carbon dioxide and formic acid are precursors of the carbons of uric acid in the pigeon. The purpose of this investigation was to determine whether these same precursors contribute carbon similarly to purines in the mammal. Advantage was taken of the fact that allantoin is excreted in the urine of the rat as the end product of purine metabolism and is readily isolated by means of a modification of the usual procedure. After administering to rats compounds labeled with radioactive carbon, allantoin was isolated from the urine, purified and degraded to determine the position of the isotope.

In the first experiment a rat was injected intraperitoneally with isotopic sodium bicarbonate hourly for 7 hours. The allantoin isolated from the urine collected during this period was found to be free from radioactivity. This was to be expected in view of the fact that while bicarbonate has been shown to be incorporated in position 6 in uric acid of pigeons, this carbon is absent in allantoin. Enough radioactive bicarbonate had been administered to cause incorporation in the purines of the body tissues.

In a second experiment, glycine, labeled in the carboxyl position with  $C^{14}$ , was mixed with the stock diet and fed to nine rats for a period of 10 days. Allantoin isolated daily from the pooled urines showed increasing concentrations of the isotope. After degradation of the allantoin the isotope was found to be incorporated in position 4. It is apparent, therefore, that glycine is utilized by the rat for purine synthesis in agreement with the earlier results obtained in the pigeon.

#### The Effects of Intravenously Administered Aminophylline on Cerebral Blood Flow in Man. RICHARD L. WECHSLER, B.S., M.D., LEE M. KLEISS, M.A., and SEYMOUR S. KETY, M.D.

(Dept. of Physiol. and Pharmacol., Grad. Sch. Med., Univ. of Penna.). It is a well known clinical fact that 0.5 gm. of aminophylline administered intravenously will stimulate the brain. It is known to make drowsy patients more alert and to make Cheyne-Stokes respirations more regular. It seemed of interest to study the effect of aminophylline on cerebral blood flow in order to help clarify its mechanism of action.

Ten patients, without any obvious cerebral depression, were chosen at random. A cerebral blood flow was performed according to the nitrous oxide method. Following this, 0.5 gm. of aminophylline in 250 cc. of physiological saline solution was administered intravenously over a period of 20 minutes. While the last 50 cc. ran in, a second cerebral blood flow was performed. Pulse, mean arterial blood pressure and respiratory rates were recorded before and during each flow.

These aminophylline studies gave the following results. There was no change in arterial  $O_2$  content. There was an expected increase in respiration reflected in a decrease in arterial  $pCO_2$  and an increase in arterial pH. There was no significant change in overall cerebral oxygen utilization. There was a striking and highly significant increase in cerebrovascular resistance which resulted in a decrease in cerebral blood flow from a mean of 59.4 to 44.4 cc. per 100 gm. per minute ( $P < .01$ ). With the decrease in cerebral blood flow and the constant cerebral oxygen utilization, the cerebral venous  $O_2$  content decreased from 8.2 to 6.2 vols.% ( $P < .01$ ). Since the cerebral venous  $O_2$  content reflects the  $O_2$  tension of the brain, aminophylline causes an anoxia of cerebral tissue.

The mechanism for these changes is obscure. As expected, hyperventilation occurred, reflected by a significant lowering of arterial  $pCO_2$  and a small rise in arterial pH. A drop in arterial  $pCO_2$

is known to cause a decrease in cerebral blood flow. The maintenance of a constant cerebral venous and therefore brain  $pCO_2$  found in this series may be the mechanism controlling the changes in cerebral circulation.

It was noted that 4 of the patients reacted to the drug with extreme anxiety and other symptoms. Each of these 4 cases had an increase in cerebral oxygen consumption, the mean being a statistically significant rise from 3.7 to 4.6 cc. per 100 gm. per min. The other 6 patients had a statistically significant decrease in cerebral  $O_2$  consumption from 3.9 to 3.3 cc. per 100 gm. per min.

These findings indicate that aminophylline, as used clinically by intravenous administration in doses of 0.5 gm., far from acting as a cerebral vasodilator, produces a marked constriction of cerebral vessels and a real anoxia of cerebral tissue as reflected in the constant and striking decrease in cerebral venous  $O_2$  content.

**Serum Esterase Levels in Alcoholic Patients.** T. C. BARNES, M.D., K. R. BEUTNER, M.D., and R. BEUTNER, M.D. (Hahnemann Med. Coll. and Hosp. of Phila., and the Keeley Institute, Dwight, Illinois). The hang-over state of chronic alcoholism and delirium tremens may be caused by a disturbance in acetylcholine metabolism.

The hepatic damage from alcohol may cause a depletion of cholinesterase, hence an excessive concentration of acetylcholine which, through its effects on the cerebral cortex might well be responsible for the disturbance of cerebral function in this ailment (as shown by abnormal fast and slow waves in EEG). (Barnes: *Confinia Neurologica*, 8, 73, 1948).

Esterase determinations were done according to a modified method of Alles and Hawes: 0.5 cc. of the blood

serum of the patient were mixed with 25 mg. acetylcholine in 20 cc.  $H_2O$  + 2 cc. buffer of pH 8, at 37°C.

The time was measured for the pH to drop from 8 to 7 (glass electrode). This esterase time is inversely related to the concentration of the esterase. No patients of over 60 years were considered since we confirmed Richter that the esterase in old age is low.

Forty-six alcoholic patients with mild or no hang-over had an esterase time value of 210 to 450 (mean  $334 \pm 7$  seconds). Forty-seven alcoholic patients with *average* or *severe* hang-over symptoms, including 2 patients with delirium tremens, had an esterase time of 180 to 1,146 seconds (average  $401 \pm 14$  seconds). The incidence of high esterase value (from low esterase content) was much higher in the severe alcoholics; there being no time values over 480 seconds (8 minutes) in the group of 47 patients with mild or no hang-over, but 10 cases in the group of 48 patients with severe or average hang-over, an incidence of 21%. It appears that the withdrawal (hang-over) symptoms of chronic alcoholism

are caused by a poisoning with endogenous acetylcholine which accumulates because of an abnormally low esterase present in the blood serum (and probably also *true* esterase).

We have found (Anat. Record, 10, 739, 1915-16) that alcohol inhibits esterase of cat brain, when macerated cat brain is allowed to act on acetylcholine. Unpublished experiments demonstrate that cat brain esterase splitting mecholyl is also inhibited by alcohol. This shows that true tissue esterase is also poisoned by alcohol.

Of the numerous empirical treatments tried for alcohol poisoning and addiction, it would seem that those are most rational which build up the depleted cholinesterase. Liver extract or folic acid seems most suitable since, according to J. E. Davis (Fed. Proc., 8, 285, 1949), they produce cholinesterase *in vivo*, as well as *in vitro* from powdered liver. We found that administration of liver extract to alcoholics produces immediate recovery, working faster than the customary  $B_1$ , or other vitamins.

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# BOOK REVIEWS AND NOTICES

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**NEURORADIOLOGY.** By ALEXANDER ORLEY, M.D., Hon. Consulting Radiologist, West End Hospital for Nervous Diseases, London. Pp. 421; 572 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, \$11.50.

This book was prepared during the war years from material largely collected from the Hurstwood Park E. M. S. Neurological Hospital. The material is presented concisely and should serve a useful purpose. The entire cerebrospinal system is included. Most of the illustrations are reproduced as positives; many do not show the radiographic detail well. The pen and pencil sketches are very helpful.

The publisher has as usual maintained his high standard of excellence in the preparation of this book. The paper is very good and the type is easy to read. E. P.

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**ATLAS OF ORAL AND FACIAL LESIONS (AND COLOR FILM LIBRARY).** By RALPH HOWARD BRODSKY, D.M.D., Consulting Oral Surgeon, Dept. of Hospitals, New York. Pp. 127; 100 figs. and 100 color lantern slides. Balt.: Williams & Wilkins, 1949. Price, \$80.00.

THE author of this publication is well known and well qualified to write on this subject. The description text for each of the 100 Kodachrome reproductions is brief yet sufficiently complete. All of the common benign lesions and neoplasms are included in this atlas, as well as some of the less common conditions. General types of treatment are discussed.

More emphasis might have been given to a discussion of differential diagnosis. While the reviewer had an opportunity to examine only 3 of the separate Kodachrome reproductions, it was readily apparent that much of the original color values had been lost in the duplication.

Students and practitioners of Dentistry and Medicine should be familiar with this atlas. L. B.

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**CURRENT THERAPY, 1949.** Edited by HOWARD F. CONN, M.D., et al. Pp. 672. Phila.: W. B. Saunders, 1949. Price, \$10.00.

This book, by 236 American Authorities, gives brief, specific methods for the treatment of practically all diseases that one is likely

to meet in medical practice. Each article gives concise directions for the use of drugs and other therapeutic measures which the author employs in his own practice. In many conditions it describes the methods used by more than one authority; usually there is but little variation in the recommendations.

The pages are large, but the double column format makes reading easy. The book is divided into 14 sections, with the appropriate diseases arranged alphabetically in each section. There is a table of contents in the front of the volume, and a complete index of subjects and of authors in the back.

This is a book for which every doctor will find daily use. H. H.

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**BIOCHEMISTRY OF THE TEETH.** By HENRY M. LEICESTER, Prof. of Biochemistry, Coll. of Phys. and Surg. of San Francisco. Pp. 306; 5 ills. St. Louis: C. V. Mosby, 1949. Price, \$5.00.

THE book opens with considerations of tooth structure such as the fact, known for a century and a half, that teeth are composed of lime salts. Recently, the use of x-rays and the electron microscope has shown that the crystal lattice structure of enamel, dentin and bone resembles the naturally occurring mineral apatite. Nevertheless the physical properties of each of these structures differ.

A chapter on tooth formation including a discussion of the mechanism of calcification follows. Enamel differs from bone in being an epithelial derivative, and its organic matrix is probably a kerato-hyalin similar to that of keratins of hair and nails. Dentin has a collagenous ground substance which subsequently becomes calcified. Unlike bone, dentin is not normally subject to the physiologic withdrawal of calcium salts. The enzyme mechanisms involved in the process of calcification of all these structures are reviewed and discussed. The effect of vitamins and of hormones on developing teeth is reviewed. Finally the application of this biochemistry information to the problem of dental caries is considered.

This book has collected the references from many fields and presented findings with a critical discussion of technical methods and sources of discrepancies and disagreements. P. B.



# NEW BOOKS

*Oncologia. Journal of Cancer Research: Prevention, Treatment and Sociological Aspect.* Edited by E. BIANCHI and P. JUNG. Basel and New York: S. Karger, 1948. Price, 30 Swiss fr. a year.

This most recent of cancer journals appears quarterly as the official organ of the Swiss National League for Krebsbekämpfung. Manuscripts are accepted in German, English, French or Italian, with a Summary in all four languages. In the number sent for review (Vol. I, No. 3) the 6 titles cover an interesting range of subjects.

*Symposium de Hematologia y Hemoterapia.* Por el Dr. J. GUASH, et al. Pp. 522; illustrated. Barcelona, Spain: Miguel Servet, 1949. Price not given.

This first volume of projected Symposia on Hematology and Hemotherapy contains 7 articles on Penicillin in the treatment of the malignant neutropenias, simple and combined, Treatment of Kala-azar by splenectomy, Constitutional elliptocytosis, Leukemia and pregnancy, Blood picture in clinical allergy, Note on the distribution of the Rh factor in Spain, Therapeutics by the bone marrow way. A summary in English of each article will guide the English speaking reader through much tiring detail.

*Biochemical Preparations, Vol. I.* Edited by HERBERT E. CARTER, et al., University of Illinois. Pp. 76. New York: John Wiley & Sons, 1949. Price, \$2.50.

The first volume of this new series is very welcome to biochemists. Many compounds of biological interest have appeared in Organic Syntheses (as recorded on p. ix of this first volume). Nevertheless, there are many other compounds needed for biochemical research which must be made by the investigators themselves. Precise directions given in sufficient detail are of great assistance to those who must make a preparation for the first time. The present volume proposes to do this and has succeeded very well. It is hoped that Biochemical Preparations will be extended rapidly.

D. W.

*Medical Latin.* By CAROLYN LEWIS. Pp. 135. Francetown, N. H.: Marshall Jones, 1948. Price, \$2.00.

*An Outline of Psychoanalysis.* By SIGMUND FREUD. Translated by JAMES STRACHEY. Pp. 127. New York: W. W. Norton, 1949. Price, \$2.00.

*Child Health Services and Pediatric Education Report of the COMMITTEE FOR THE STUDY OF CHILD HEALTH SERVICES, THE AMERICAN ACADEMY OF PEDIATRICS.* Pp. 270. New York: Commonwealth Fund, 1949. Price, \$3.50.

"A nation-wide survey, the first that has ever been undertaken, of all the services and facilities currently available for the medical care and health supervision of infants and children throughout the country . . . and an analysis of present-day pediatric education."

*Mayo Clinic Diet Manual.* By COMMITTEE ON DIETETICS OF THE MAYO CLINIC. Pp. 329. Phila.: W. B. Saunders, 1949. Price, \$4.00.

This is one of the best diet manuals written for the physician and dietician. Complete dietary programs for various medical and surgical conditions are outlined. Vitamin, caloric, and mineral requirements and values are given and quantities are listed in household equivalents and metric weights. An excellent section on pediatric dietetics is included.

G. R

*Pancroepatías Agudas no Dramáticas.* Vols I and II. Por ALFONSO ABELLAN AYALA. Pp. 32, 67. Barcelona, Spain: Col. Española de Monograf. Méd., Edic. Byp, 1949. No price given.

*Mr. President—How Is Your Health?* By KARL C. WOLD, M.D. Pp. 214. St. Paul and Minneapolis: Bruce Publishing Co., 1948. Price, \$3.00.

DESPITE all that has been written about the lives of our Presidents, this is apparently the first attempt to set down their medical histories—30 presidents from Washington to F.D.R. Especially for the earlier presidents, a great deal is necessarily conjectural—even Washington's much discussed last illness—but the author has showed the courage of his convictions in almost always offering a definite diagnosis. His Final Analysis offers some interesting factual light on the effects on health of the responsibilities of this high office.

E. K.

## NEW EDITIONS

*Practical Bacteriology, Hematology and Parasitology.* By E. R. STITT, M.D., PAUL W. CLOUGH, M. D., and SARA E. BRANHAM, M. D. 10th ed. Pp. 991; 765 ills, many in color. Phila.: Blakiston, 1948. Price, \$10.00.

NEITHER the clinical pathologist nor the laboratory technician needs any introduction to this old stand-by. The present edition is very well prepared with good coverage of all phases of routine work in the clinical laboratory. The illustrations are well chosen and easily understood.

A. R.

*Introduction to Physiological and Pathological Chemistry.* By L. EARLE ARNOW, PH.D., PH.D., M.D., Director of Research, Sharp & Dohme. 3d ed. Pp. 595; 144 ills. St. Louis. C. V. Mosby, 1949. Price, \$4.00.

*Clinical Case-Taking.* By GEORGE R. HENRY, M.D., PH.D., Prof. of Medicine, Univ. of Texas. 4th ed. Pp. 240. St. Louis: C. V. Mosby, 1949. Price, \$3.50.

*Human Biochemistry.* By ISRAEL S. KLEINER, PH.D. 2d ed. Pp. 649; 77 ills., 5 color plates. St. Louis: C. V. Mosby, 1948. Price, \$7.00.

KLEINER's Human Biochemistry has been enlarged by about 75 pages. Many of the errors of the first edition have been corrected. A new chapter on Chemical Structure in relation to Biological Phenomena has been added. The references to clinical conditions are to be commended.

D. W.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1949

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## ORIGINAL ARTICLES

### THE ABSORPTION OF GOLD FROM PELLETS OF GOLD SALTS (AUROTHIOGLYCOLANILIDE) IMPLANTED SUBCUTANEOUSLY AND INTRAMUSCULARLY: ITS APPLICATION IN THE TREAT- MENT OF 6 CASES OF RHEUMATOID ARTHRITIS

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(From the Department of Medicine and the Arthritis Service and Department of Pathology  
[Dr. G. H. F.] of St. Margaret Memorial Hospital and the John C. Oliver Memorial  
Research Foundation of the St. Margaret Memorial Hospital)

*THIS* report describes our preliminary observations on the absorption of gold from pellets of a gold salt, Lauron (aurothioglycolanilide), implanted subcutaneously and intramuscularly in rabbits and our subsequent observations in 6 cases of rheumatoid arthritis.

The primary object of our studies was to ascertain whether pellets of gold salts implanted subcutaneously or intramuscularly could be effectively substituted in chrysotherapy for repeated injections of aqueous or oily suspensions of gold. Specifically, it was the aim of the present investigation to determine the feasibility of utilizing a depot of gold in the treatment of rheumatoid arthritis, which could be readily removed in the event that a toxic reaction developed; to determine whether implanted pellets of gold would be

tolerated by the tissues locally; whether absorption of gold would occur from such implanted pellets; and whether therapeutically effective results could be demonstrated clinically with this mode of therapy. It is evident that if such a mode of administration were feasible it would increase the safety of chrysotherapy. The patient could be spared the discomfort and inconvenience of weekly intramuscular injections. Perhaps the absorption of therapeutically effective amounts of gold over long periods of time might be more even and continuous, a likely and simple means of extending the period of gold therapy so that the likelihood of clinical relapse might be reduced.

Although our studies are as yet in many respects incomplete and are being extended, we feel that the results

obtained thus far both in experimental studies on rabbits and in the study of 6 patients with rheumatoid arthritis are sufficiently interesting and potentially significant to warrant publication of our present observations so that further study by other observers, as well as ourselves, may help to crystallize the practical advantages of this mode of chrysotherapy in rheumatoid arthritis.

Since the introduction of gold therapy<sup>10</sup> for rheumatoid arthritis 20 years ago and the pointed observations of Forestier<sup>6</sup> indicating the striking effectiveness of chrysotherapy in this disease, various studies relating to the effectiveness of gold salts in thousands of cases of rheumatoid arthritis have been published<sup>9</sup>. Although results vary widely, approximately 55% of the patients may be expected to become symptom-free or notably relieved; approximately 13% obtain complete remissions for periods ranging from 45 to 78 months<sup>11</sup>. Controlled investigations show that the results of chrysotherapy in rheumatoid arthritis are actually referable to the pharmacologic effect of gold<sup>5</sup>.

Our own experience with chrysotherapy in several hundred cases of rheumatoid arthritis confirms Hench's conclusions<sup>8</sup> that, in addition to other well accepted general measures of systemic therapy, "chrysotherapy is superior to any other treatment and is the only method which will markedly change the course of the disease in a significant percentage of patients."

The real drawback to the most widespread employment of gold therapy in rheumatoid arthritis has been the occurrence of reactions of varying degrees of severity in approximately 40% of patients treated. Most of these reactions are mild, but some are serious and, in approximately 0.4% of cases, they are fatal<sup>5</sup>. In some few cases reactions to gold may develop after administration of small amounts of the drug, appar-

ently because of an inherent hypersensitivity of the individual. In the majority of instances, however, reactions are the result of the cumulative action of the drug. This is especially true of cases with severe, protracted, or fatal reactions. The most serious of these are generalized exfoliative dermatitis, agranulocytosis, purpura, acute hepatitis, nephritis, and nephrosis. Various means have been suggested to reduce the incidence of such reactions. As a result of the metabolic studies of Freyberg and his associates<sup>7</sup> the dosage of gold (which in earlier years of chrysotherapy was large, ranging from 100 to as much as 400 mg. of the gold salt at each injection) has been reduced. The majority of physicians with wide experience in chrysotherapy now administer individual doses no larger than 50 mg. of the more soluble gold salts containing approximately 50% of gold<sup>3</sup>. Such lowered dosage has reduced but not eliminated the incidence of severe reactions. Further measures have become available with which we may combat some effects of gold toxicity. Boland, Headley, and Hench<sup>2</sup> have indicated the effectiveness of penicillin in the treatment of a case of agranulocytosis resulting from chrysotherapy. The effectiveness of British Anti-Lewisite (BAL) for either ameliorating or controlling toxic reactions has also been demonstrated<sup>4</sup>. Despite these distinct advances, the control of serious reactions is still the most difficult and harassing problem attending chrysotherapy.

In our own experience with patients presenting severe toxic effects of gold, we have been especially impressed with the difficulty inherent in the fact that such patients must contend not only with the gold circulating in the plasma and that stored in the tissues, but also with depots of gold which remain at the sites of the original injection. It has appeared to us unfortunate that a patient contending with the toxic effects

of gold should at the same time have to contend with additional absorption of the same metal from depots over which we have, in the past, had no control. To try to develop practical means for the elimination of gold salts from depots at the site of administration of the drug, so that further absorption from them could be entirely eliminated if a toxic reaction developed, seemed eminently desirable.

It was with this goal in mind that experiments with pellets of gold were undertaken. Since it was our intention to create a depot from which gold

aration of the pellets. Those used for the initial studies in rabbits weighed 200 mg., approximately equivalent to a human dose of 5 gm.; they measured approximately 0.65 cm. in diameter by 0.3 cm. in thickness. The pellets used for implantation into patients weighed 850 to 865 mg. each; they measured 1.15 cm. in diameter by 0.55 cm. in thickness.

**EXPERIMENTAL STUDIES IN RABBITS.** Seven rabbits were used for implantation of pellets of Lauron. In all instances, plasma gold determinations checked prior to implantation were

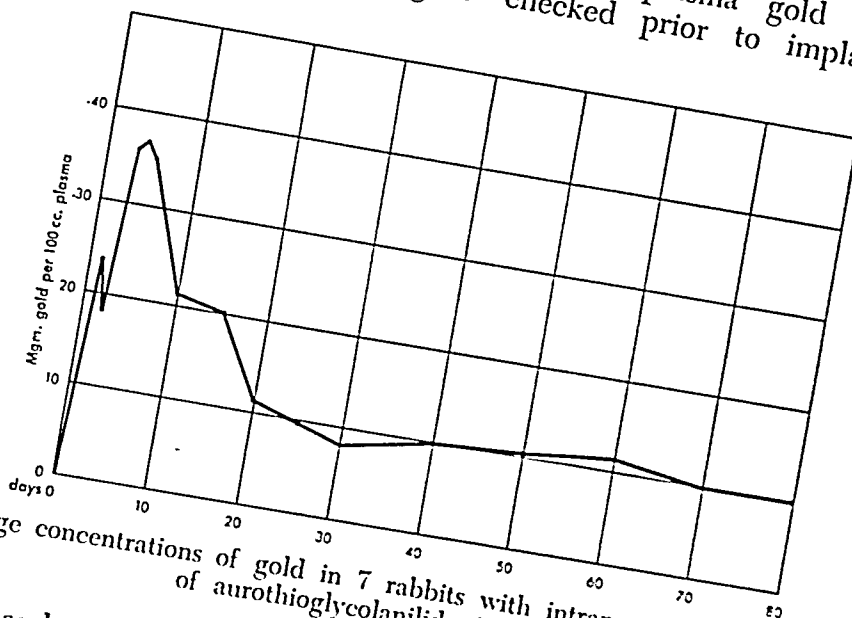


FIG. 1.—Average concentrations of gold in 7 rabbits with intramuscularly implanted pellets of aurothioglycolanilide (Lauron).

would be absorbed slowly and over a long period of time, our present observations relate to a relatively insoluble preparation of gold namely, Lauron (aurothioglycolanilide).<sup>\*</sup> The pellets were made by compression of the powdered salt of aurothioglycolanilide and sterilized by a high pressure autoclave. The Lauron powder consisted of particles 5 to 10 micra in diameter, representing a compound with a melting point of 253 to 254 centigrades, containing 54.6% of gold. No binding material was used in the preparation.

<sup>\*</sup> This material was supplied through the kindness of Dr. Lewenstein of Endo Products Company.

negative. Under intravenous pentothal anesthesia, the skin over the shoulder girdle on one side was shaven and prepared with zephirin. Under aseptic technique, a pellet of Lauron weighing 200 mg. was implanted into the subscapular muscle. Several catgut sutures were used to close the muscle and skin.

Plasma gold determinations were performed by the method of Block and Buchanan<sup>1</sup>. They were made daily for 5 to 6 days following implantation of the pellets, then every 2 to 3 days, then

the pellets, then every 2 to 3 days, then

about once weekly. Six rabbits were sacrificed or died of causes unrelated to the experiment from 17 to 68 days after the implantation of the pellets. As indicated in Fig. 1, the plasma gold

curve followed a fairly constant pattern in all 7 rabbits. The plasma gold concentration reached a peak of from 0.25 mg. to 0.975 mg. per 100 cc. within the first 6 days following implantation of

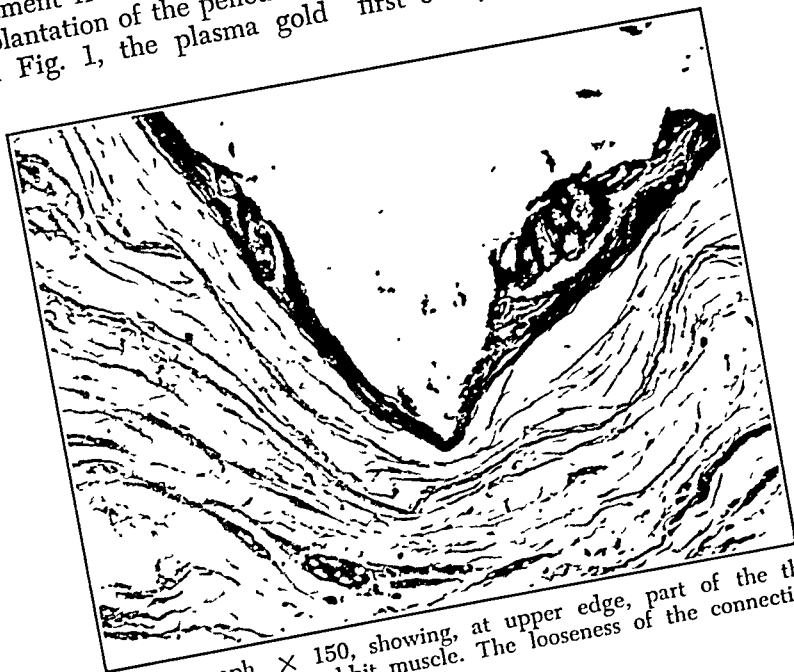


FIG. 2.—Photomicrograph,  $\times 150$ , showing, at upper edge, part of the thin membrane which encased a gold pellet in rabbit muscle. The looseness of the connective tissue peripheral to the membrane is well illustrated.

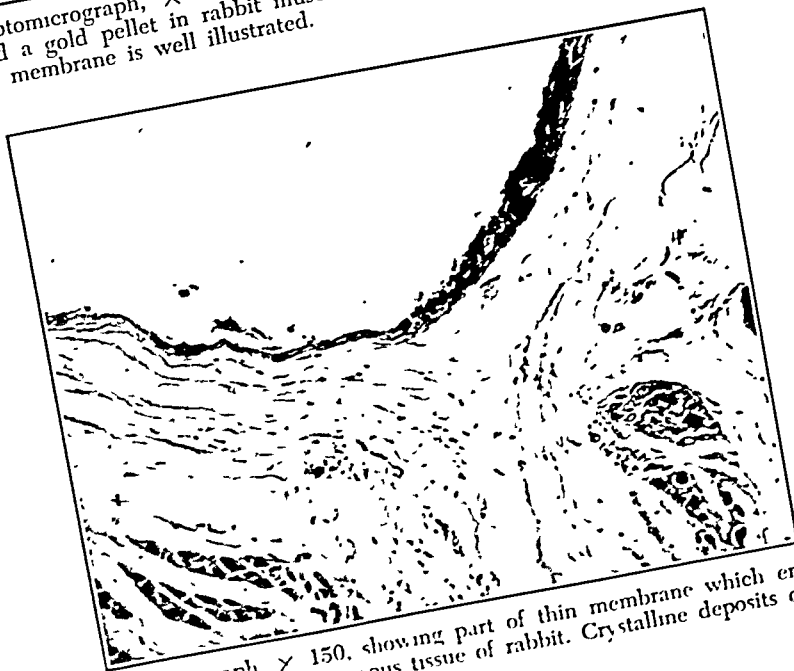


FIG. 3.—Photomicrograph,  $\times 150$ , showing part of thin membrane which enclosed a gold pellet which came to lie in subcutaneous tissue of rabbit. Crystalline deposits of Lauron may be seen within the fibrous membrane.

the pellets. Thereafter the plasma gold level gradually dropped to a concentration varying between 0.075 mg. and 0.125 mg. per 100 cc. In 2 of the 7 rabbits, however, plasma gold levels as high as .175 and .15 mg. were obtained as long as 32 and 40 days after implantation, respectively. The average plasma gold level was 0.154 mg.

One rabbit is still being observed 17 months after implantation of the pellet. Plasma gold concentrations in this rabbit have been maintained at between .05 mg. and .125 mg. per 100 cc. for

the pellet could easily be shelled out when this envelope was incised (Figs. 2 and 3).

**CLINICAL INVESTIGATION.** Six patients with rheumatoid arthritis, none of whom had previously received any type of gold therapy, were selected for implantation of pellets of Lauron\*. In all instances control plasma gold determinations prior to implantation of the pellets of Lauron were negative.

**Case Reports.** CASE 1. T. D., white male, age 58, suffered from an active rheumatoid arthritis involving most of the joints which had

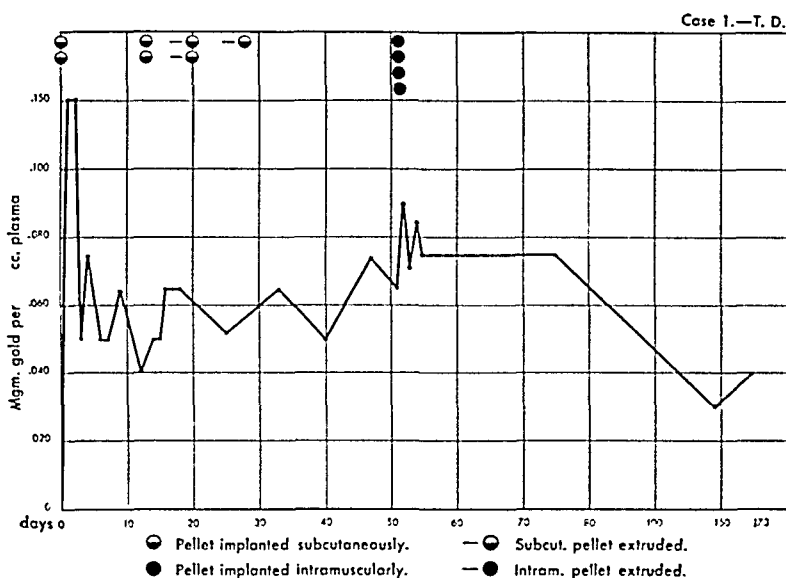


FIG. 4.—Plasma concentration of gold in Case 1 (T. D.) after subcutaneous and intramuscular implantation of pellets of aurothioglycolanilide (Lauron).

as long as 380 days following implantation. Postmortem examination was done on 6 rabbits at 17, 22, 32, 40, 66, and 68 days respectively, after implantation of the pellets. In one rabbit the pellet was still found in the substance of the muscle; in the other 5, the pellets were lying either under the muscle sheath, outside the body of the muscle, or in the overlying subcutaneous tissue. In all instances the pellet was found to be encased in a semi-translucent envelope of fibrous connective tissue from which

developed abruptly 3 months previously. He also suffered from chronic bronchiectasis which had been present for many years. He presented marked stiffness and soreness of joints, synovial swelling of the hands, elbows, and knees, and edema of the ankles. The sedimentation rate was accelerated to 24 mm. in 30 minutes and 26.5 mm. in 60 minutes (Cutler Method); the blood count showed a hypochromic anemia; the urinalysis was normal. Roentgenograms of the hands, wrists, shoulders, and ankles revealed typical early rheumatoid changes.

On March 13, 1948, 2 pellets of Lauron, each weighing 850 mg., were implanted subcutaneously in 2 separate sites in the lower

\* We are indebted to Dr. James R. Watson and Dr. D. N. DiSilvio for the surgical implantation of the pellets.

abdominal wall. These 2 pellets were broken during the course of implantation. On March 26, 1948, 2 additional pellets, each weighing 865 mg., were implanted subcutaneously in separate sites in the upper abdominal wall. There was a continuous serous discharge from these sites with extrusion of fragments of 3 pellets, 1 remaining intact. On May 3, 1948, 4 more pellets, 2 into each side, were implanted into the substance of the sternal portion of the pectoralis major muscles. These incisions healed *per primum* and the pellets stayed intact. Approximately 4.3 gm. of gold remained *in situ*.

The usual systemic measures of treatment, which included 2 blood transfusions of 500 cc. each, and physiotherapy, were also employed.

til the 173rd day, at which time the level was 0.04 mg. The average plasma gold level was 0.068 mg. per 100 cc.

The clinical improvement of this patient occurred slowly but progressively in the course of the 5 months of observation. The synovial swelling of the hands, elbows, and knees largely subsided, the ankle edema disappeared, and the subjective stiffness and pain were considerably ameliorated. The sedimentation rate, however, remained about the same.

CASE 2. S. L., white female, age 44, had rheumatoid arthritis of 4½ years' duration.

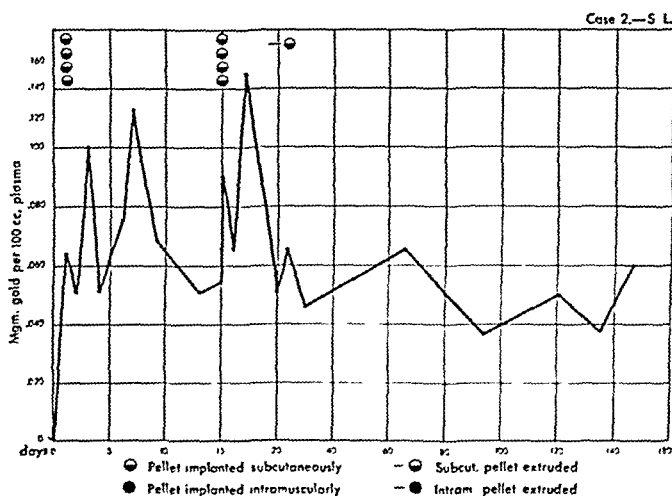


FIG. 5.—Plasma concentration of gold in Case 2 (S. L.) after subcutaneous implantation of pellets of aurothioglycolanilide (Lauron).

There was an initial rise in the plasma gold concentration (Fig. 4) to .15 mg. for 2 days following implantation of the first 2 pellets, when the plasma gold level gradually fell to .04 mg. on the 12th day when 2 additional pellets were implanted subcutaneously. Despite the extrusion of 3 of the 4 pellets, the plasma gold level remained between .05 and .075 mg. Following implantation of 4 additional pellets intramuscularly the plasma gold concentration rose to .09 mg. and for the next 5 days varied between .07 and .085 mg., finally being maintained at .075 mg. un-

There was moderate capsular and synovial swelling at the finger joints and wrists, slight atrophy of the interosseous muscles of the hands, mild synovial swelling of the knees, stiffness of the shoulders, and tenderness and swelling of the feet. The sedimentation rate was 10 mm. in 30 minutes; 19 mm. in 60 minutes (Cutler Method). The blood count and urinalysis were normal. Roentgenograms of the hands revealed characteristic changes of rheumatoid arthritis. On March 23, 1948, 4 pellets of Lauron, 2 into each site, were implanted into the subcutaneous tissue of the lower abdominal wall. Three of the pellets contained 850 mg. of Lauron, the fourth, 865 mg. On April 7, 1948, 4 additional pellets, each containing 865 mg. of Lauron, 2 pellets at each site, were implanted at 2 separate

sites into the subcutaneous tissues of the upper abdomen. There was persistent serous drainage from the 2 sites of implantation in the lower abdomen, and 1 pellet was extruded in pieces, following which the incisions healed. The 4 pellets in the upper abdomen remained intact, the incisions healing promptly. The 7 pellets remaining *in situ* totaled approximately 6.0 gm.

As indicated in Fig. 5, there were marked fluctuations in the plasma gold concentration following implantation of the first 4 pellets of Lauron with levels as high as .10 and .125 mg. per 100 cc. on the 3rd and 7th days and as low as .05 mg. on the 2nd, 4th, and 13th days

plantation of Lauron, it was 2 mm. in 30 minutes, 5 mm. in 60 minutes (Cutler Method). The blood count and urinalysis remained normal.

CASE 3. O. E., white male, age 55, had chronic rheumatoid arthritis of 1½ years' duration. There were characteristic rheumatoid changes with synovial swelling in the hands, knees, and ankles, as well as limitation of motion in both shoulders. The sedimentation rate was 10 mm. in 30 minutes; 18 mm. in 60 minutes (Cutler Method). The blood count and urinalysis were normal. Roentgenograms of the hands showed typical rheumatoid arthritic changes.

On April 12, 1948, 6 pellets of Lauron,

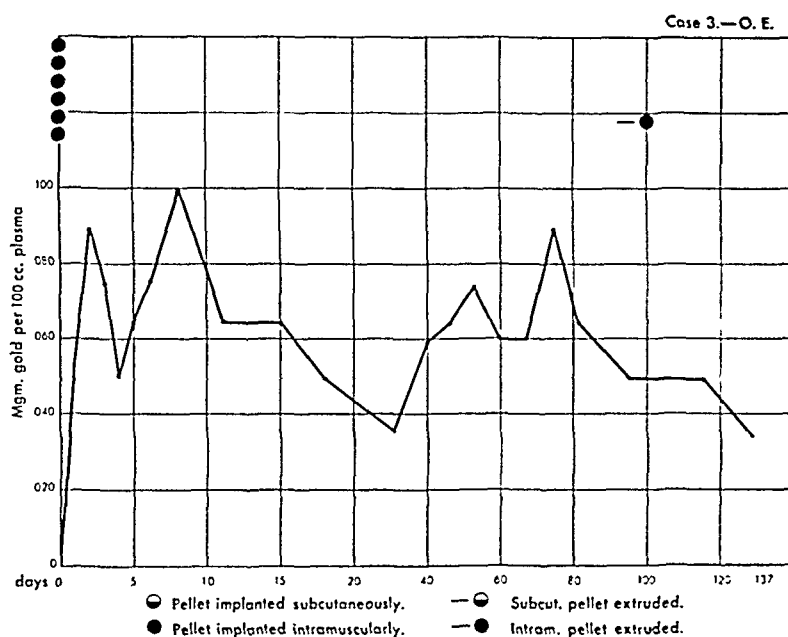


FIG. 6.—Plasma concentration of gold in Case 3 (O. E.) after intramuscular implantation of pellets of aurothioglycolanilide (Lauron).

following implantation. After implantation of 4 additional pellets the plasma gold concentration rose to .15 mg. and varied thereafter between .065 and .0375 mg. The average plasma gold level was 0.069 mg.

The patient showed striking progressive improvement, both subjectively and objectively. The pain and synovial swelling subsided completely and the range of motion in the joints returned to normal. The sedimentation rate paralleled the clinical improvement; on September 16, 1948, 6 months after im-

865 mg. each, totaling 5.19 gm. in all, were implanted into the substance of the internal oblique muscle in the right flank. Serous drainage from the wound persisted until July 2, 1948, when the incision closed completely. The pellets remained intact at the site of implantation until July 21 (100 days following implantation) when one corner of the incision opened and fragments of a pellet were extruded. Thereupon the incision again closed. The remaining pellets totaled approximately 4.3 gm.

Following implantation of the pellets of Lauron the plasma gold concentration ranged from .0375 to .10 mg. per 100 cc., but in general tended to re-



main between .05 and .075 mg. for the period of observation of 137 days. (Fig. 6.) The average plasma gold level was 0.063 mg.

There has been striking and progressive improvement in the arthritis, the swelling has largely subsided, the joints have become more flexible, and the pain has diminished. The blood count and urinalysis have continued to be normal, and the sedimentation rate on June 4, 1948, was 7 mm. in 30 minutes; 15 mm. in 60 minutes (Cutler Method).

More recently, 3 additional patients with rheumatoid arthritis had pellets of Lauron implanted intramuscularly into the substance of the internal oblique and transversalis muscles. As in the first group, control plasma gold determinations prior to implantation of the pellets were negative.

The operative technique in the more recent 3 cases was as follows: A right oblique flank incision was made and carried through the aponeurosis of the external oblique muscle. Six individual pockets were made in the internal oblique and transversalis muscles and one pellet of Lauron was introduced into each pocket. The individual pockets were oversewn with interrupted fine chromic catgut sutures. The aponeurosis of the external oblique muscle was then overlapped over the internal oblique muscle with interrupted chromic catgut sutures. The subcutaneous tissue was approximated with fine catgut and the skin was closed with silk. The latter was removed at the end of 10 days.

Since this group of 3 patients has been observed for a period of only 2 months, we will not attempt evaluation of the clinical results, but will only indicate the plasma gold levels obtained thus far.

CASE 4. M. S., white female age 76, suffered from an active, early rheumatoid arthritis involving chiefly the hands and knees, which had begun rather abruptly 2 months

previously, during convalescence from a radical mastectomy. There was marked synovitis of both knees and stiffness and soreness of the metacarpophalangeal and proximal interphalangeal joints of both hands. There was also marked pitting edema of both legs, hypoproteinemia, a marked hypochromic anemia, moderate essential hypertension, and generalized arteriosclerosis. The sedimentation rate was accelerated at 27 mm. in 30 minutes and 29 mm. in 60 minutes (Cutler Method). The urinalysis showed grade 1 albuminuria. Except for moderate osteoarthritis, such as might be expected in a person of this age, roentgenograms of the knees were negative. Roentgenograms of the hands showed generalized osteoporosis.

The patient was hospitalized. Blood transfusions and the usual systemic measures of treatment and physiotherapy were instituted.

On August 23, 1948, 6 pellets of Lauron, each weighing 850 mg. and totaling 5.1 gm. in all, were implanted intramuscularly. The incision healed *per primum* and the pellets remained intact.

The patient has been followed for 31 days, during which time the plasma gold concentration has ranged from .03 to .05 mg., with an average level of .039 mg.

CASE 5. E. C., white female, age 44, was first seen in December, 1945, with rheumatoid (psoriatic) arthritis of 3 months' duration, accompanied by a hypochromic anemia and accelerated sedimentation rate. The psoriatic lesions were minimal.

In addition to general systemic measures, the patient was started on treatment with a soluble gold preparation, Solganol B Oleosum (Schering), a total of approximately 520 mg. being given over a period of 5 months, with marked improvement in the arthritis.

The patient was not seen again until July, 1948, at which time an exacerbation of the arthritis had developed with involvement of the elbows, shoulders, knees, ankles, and feet. There was synovial swelling of the metacarpophalangeal and proximal interphalangeal joints of the hands and the knees, capsular swelling of the distal interphalangeal joints of the toes, and stiffness of the shoulders. The sedimentation rate was 22 mm. in 30 minutes and 27 mm. in 60 minutes (Cutler Method). There was a moderate hypochromic anemia. The urinalysis was normal; roentgenograms of the hands were negative. The plasma gold determination was negative.

On August 23, 1948, 6 pellets of Lauron each weighing 850 mg. and totaling 5.1 gm. in all, were implanted intramuscularly. The incision healed, *per primum*. On Sep-

tember 15, 1948, however, 23 days following implantation, there was a slight separation of the lower corner of the incision with drainage of a small amount of serum, which has persisted. The patient has been observed for 35 days, during which the plasma gold determinations have ranged from .035 to .065 mg., with an average level of .045 mg. A roentgenogram of the site of implantation revealed that all 6 pellets were intact (Fig. 7).

CASE 6. A. M., white male, age 39, had a rheumatoid arthritis of 8 years' duration.

of the hands and feet showed characteristic rheumatoid changes.

On September 10, 1948, 8 pellets of Lauron, each weighing 850 mg. and totaling 6.8 gm. in all, were implanted intramuscularly. The incision healed *per primum* and the pellets have remained intact. Skin grafting over the varicose ulcers was performed at the same time.

Plasma gold levels during the 13 days following implantation of the pellets have ranged from .04 to .08 mg., with an average level of .055 mg.

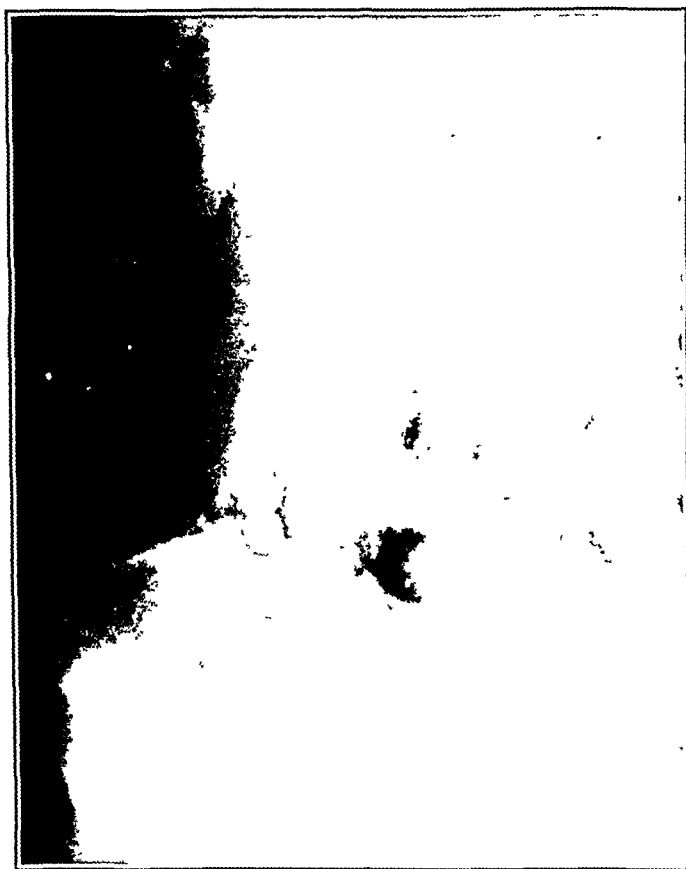


FIG. 7.—Roentgenogram showing 6 pellets of aurothioglycolanilide (Lauron) implanted intramuscularly.

There was slight synovial swelling of the metacarpophalangeal joints of the hands, characteristic flexion and ulnar deviation of the hands, tenosynovial swelling over the wrists, rheumatoid nodules at the proximal phalangeal joints and along the extensor aspects of both forearms, and mild rheumatoid deformities of the feet. He also presented varicose ulcers of both ankles. The sedimentation rate was accelerated to 18 mm. in 30 minutes and 23 mm. in 60 minutes (Cutler Method); the blood count and urinalysis were normal. Roentgenograms

**Summary and Conclusions.** We are continuing observations on implanted pellets of Lauron (aurothioglycolanilide) in a larger group of patients with rheumatoid arthritis. Further investigation will also be directed toward ascertaining the optimum dose of gold to be implanted, the best sites for implantation, and further means for overcoming the apparently irritating foreign-

body reaction induced by some implants, which leads to their extrusion.

The results of the present investigation, details of which have just been described, may be summarized as follows:

Pellets of Lauron (aurothioglycolanilide) implanted either subcutaneously or intramuscularly in rabbits were generally well tolerated by the tissues. In 3 of the 6 clinical cases there was some drainage of serum from the wound for several weeks after subcutaneous implantation of the pellets, apparently the result of a foreign-body reaction of the tissues. Eventually, however, the wounds healed completely. Some of these pellets were extruded either in part or as a whole. Other pellets implanted subcutaneously did not produce serous drainage and were retained. The intramuscular implantation of Lauron pellets was tolerated better than the subcutaneous. The improved

operative technique employed in the last 3 cases appears to have reduced the tendency to extrusion of the implanted pellets. In none of the cases was there evidence of local pain or infection resulting from the implantation. The plasma gold concentration increased abruptly shortly after the implantation of the pellets; then dropped to a lower level, which was maintained more or less constantly throughout the entire period of observation ranging from 3 to 5 months. These findings indicate that the subcutaneous or, better, intramuscular implantation of pellets of gold constitutes a practical procedure which might be further refined and developed for the clinical management of rheumatoid arthritis.

It is to be noted that the plasma gold concentration obtained in the rabbits as well as in the 6 patients studied were considerably lower than the plasma gold levels found in the studies of

TABLE 1.—PLASMA CONCENTRATIONS OF GOLD AFTER IMPLANTATION OF PELLETS OF AUROTHIOGLYCOLANILIDE (LAURON) FROM 1ST TO 179TH DAY OF OBSERVATION IN FIRST 3 CASES STUDIED.

| Days | Mg. of Gold per 100 cc. of Plasma |              |              | Days    | Mg. of Gold per 100 cc. of Plasma |              |              |
|------|-----------------------------------|--------------|--------------|---------|-----------------------------------|--------------|--------------|
|      | Case 1—T. D.                      | Case 2—S. L. | Case 3—O. E. |         | Case 1—T. D.                      | Case 2—S. L. | Case 3—O. E. |
| 1    | .152                              | .065         | .05-.055     | 40      | .05                               |              |              |
| 2    | .152                              | .05          | .09          | 46      |                                   |              | .065         |
| 3    | .05                               | .10          | .075         | 47      | .075                              |              |              |
| 4    | .075                              | .05          | .05          | 51      | .065-.09                          |              |              |
| 5    |                                   | .065         | .065         | 52      | .07-.075                          |              |              |
| 6    | .05                               | .075         | .075         | 53      | .07                               |              | .075         |
| 7    | .05                               | .125         |              | 54      | .085                              |              |              |
| 8    |                                   | .09          | .10          | 55      | .075                              |              |              |
| 9    |                                   | .065         |              | 58      | .075                              |              |              |
| 10   | .65                               |              |              | 60      |                                   |              | .06          |
| 11   |                                   |              | .065         | 65      |                                   | .065         |              |
| 13   | .01                               | .05          |              | 67      |                                   |              | .06          |
| 14   | .05                               |              |              | 75      | .075                              |              | .09          |
| 15   | .05                               | .055-.065    | .065         | 81      |                                   |              | .065         |
| 16   | .065                              | .065         |              | 94      |                                   | .0375        |              |
| 17   | .065                              | .075         |              | 95      |                                   |              | .05          |
| 18   | .065                              |              | .05          | 116     |                                   |              | .05          |
| 19   |                                   | .15          |              | 121     |                                   | .05          |              |
| 20   |                                   | .05          |              | 135     |                                   | .0375        |              |
| 23   |                                   | .065         |              | 137     |                                   |              | .0375        |
| 25   | .055                              |              |              | 145     | .03                               |              |              |
| 30   |                                   | .015         | .0375        | 173     | .01                               |              |              |
| 33   | .065                              |              |              | 179     |                                   | .08          |              |
| 39   |                                   |              | .06          | Average | .068                              | .069         | .063         |

Freyberg<sup>7</sup> with accepted therapeutic doses of *soluble gold* preparations injected intramuscularly. The average plasma gold concentration in our first 3 cases with implanted pellets of Lauron was 0.067 mg. (Table 1). The average plasma gold concentration obtained by Freyberg after the injection of weekly doses of 50 mg. of gold sodium thiomalate (25 mg. of gold) given intramuscularly was 0.33 mg., 5 times higher than the average plasma gold level obtained by us. If the clinical improvement in the first 3 cases observed by us were really the result of the gold therapy employed, and not the result of spontaneous remission (a possibility, of course) there is a real question whether the higher plasma gold levels noted by Freyberg with intramuscular injections of soluble gold preparation are really the minimum levels necessary for therapeutic results. It seems to us a simple possibility that lower plasma gold concentrations may be as effective therapeutically as the higher ones obtained presently with the commonly accepted dose of 50 mg. of soluble gold salts. Such a possibility is implicit in the report of Rawls and his associates<sup>12</sup> who obtained satisfactory therapeutic results in the treatment of rheumatoid arthritis with doses of gold ranging from 5 to a maximum of 25 mg. of the gold salt, doses much smaller than those currently employed. Obviously further review of the question of dosage with preparations of soluble gold salts is indicated. Such smaller doses, if accompanied by satisfactory therapeutic results, would present a distinct advance in chrysotherapy of rheumatoid arthritis, for it would probably again reduce the incidence of severe reactions by reducing storage, thereby reducing the likelihood of protoplasmic poisoning. The possibility exists that the lower plasma gold levels obtained

with implanted pellets may be more effective therapeutically because of the more constant, more even, and more continuous absorption, and more constant maintenance of the therapeutic level from the pellets as compared with the intermittent and perhaps irregular absorption of gold from intramuscular injections given at intervals of a week.

In addition to the advantage of having a readily removable depot of gold, there is the additional advantage of the patient's not requiring weekly visits for injection of the drug, thus providing not only an effective, but convenient and economical form of chrysotherapy.

Although the number of cases reported in this preliminary report is so small that conclusive remarks concerning the therapeutic efficacy of pellets of gold cannot be made, and are not attempted at this time, it may be significant that in the 3 instances reported which have been observed for periods up to 7 months, there was striking subjective and objective evidence of improvement in the clinical condition of all patients, and simultaneous lowering of the sedimentation rate in 2. Our extensive experience with chrysotherapy would suggest that the clinical improvement noted was probably influenced by the gold therapy. We are aware of the fact that spontaneous remissions occur in rheumatoid arthritis and that the cases studied are few. Hence we are not ready to draw definitive conclusions concerning the therapeutic efficacy of implanted pellets of gold. These will have to await more extensive investigation on a large number of patients. The present report would indicate, however, that further investigation of this problem is distinctly justified, since it may supply a new, and possibly most effective and least hazardous, means for the therapeutic utilization of gold in the management of rheumatoid arthritis.

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# THE TREATMENT OF PNEUMONIA AND OTHER INFECTIONS WITH A SOLUBLE SULFONAMIDE, GANTROSAN (NU-445; 3, 4-DIMETHYL-5-SULFANILAMIDO-ISOXAZOLE)

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THE sulfonamides continue to be of value in the treatment of certain infections, even though they have been partially displaced by the antibiotics. One of the chief drawbacks to the employment of the sulfonamides, however, has been the development of urinary calculi as a result of precipitation of the drug in the tubules and pelves of the kidneys and in the ureters. Measures commonly used to keep the concentration of the drug below the saturation level in the tubular urine, such as the forcing of fluids and alkalinization, are frequently neither practical nor dependable. The employment of sulfonamide mixtures according to the method of Lehr<sup>5</sup> is often effective in preventing the development of calculi, but introduces the possibility of an increased hazard of sensitization. For all these reasons, a more soluble drug would be welcome.

Gantrosan (3, 4-dimethyl-5-sulfanilamido-isoxazole)\* is a sulfonamide of comparatively high solubility†. At a

pH of 6.0 it is soluble to the extent of 350 mg. per 100 cc. as compared with less than 60 mg. per 100 cc., or less, for sulfadiazine and sulfamerazine. The acetylated salt of gantrosan at pH 6.0 is soluble to the extent of 110 mg. per 100 cc. as compared with 80 mg. per 100 cc., or less, for acetylated sulfadiazine and sulfamerazine. *In vitro* and in animals gantrosan has been found to resemble sulfadiazine in therapeutic activity. In view of these facts, we have studied the effectiveness of the drug in human infections and are reporting results of this study in the present paper.

**Plan of Study.** Gantrosan was available to us in 0.5 gm. tablets for oral use and in 10 cc. ampules containing 1 gm. of the lithium salt for intravenous, subcutaneous or intramuscular administration. The lithium salt was given in a 10% solution subcutaneously or intramuscularly. When we administered it intravenously, we diluted it with isotonic salt or with glucose solutions, although it can be given without dilution.

For most infections we gave an initial dose of 6 gm. followed by 1 gm. every 4 hours.

\* Supplied by Hoffmann-LaRoche, Inc., Nutley, New Jersey.

† At pH of 6 the solubility is 1/5 that of sulfanilamide, but at pH of 6.2 it is over 1/2 as soluble and probably reaches its solubility at a slightly higher pH. Since sulfanilamide has such a limited therapeutic range, the comparison has been made only to those drugs commonly in use.

For urinary tract infections, 2 gm. were given initially and 1 gm. every 4 hours thereafter. Comatose patients were given 6 gm. intravenously followed by 3 gm. by subcutaneous injection every 8 hours until they could be placed on the usual oral dose. If this could not be done within 24 or 36 hours, 1 gm. was administered by stomach tube every 4 hours. Children were given doses proportionate to their ages on the basis of 0.06 gm. per pound of body weight for each 24 hour period,  $\frac{1}{2}$  of the 24-hour dose being given as the initial dose.

Alkalies were not administered, nor were fluids forced. The amount of fluids given to each patient was the same as he would have received if he had not been receiving sulfonamides.

*Concentration of gantrosan in blood and cerebrospinal fluid.* The concentration of the drug was determined by the method of Marshall and Bratton<sup>1</sup> modified for the use of the spectrophotometer. At first the concentrations of both total and free gantrosan were determined, but it was soon evident that very little conjugation took place. The values for total gantrosan were the same or, at the most, 25% more than the values for the free drug. Accordingly, in the great majority of instances tests were made for free gantrosan only.

Table 1 shows the free gantrosan concentrations in 4 adult subjects at various intervals after a single oral dose of 6 gm. It is apparent that a high con-

the blood 12 hours after the single oral dose.

In Table 2 are given the free gantrosan concentrations in 4 subjects who received a single intravenous dose of 6

TABLE 2.—FREE BLOOD CONCENTRATIONS OF GANTROSAN AFTER THE INTRAVENOUS ADMINISTRATION OF 6 GRAMS

| Subject | Concentration of Gantrosan (mg. per 100 cc.)<br>Hours after Administration |     |     |
|---------|--|-----|-----|
|         | 1  | 4   | 8   |
| C. H.   | 10.6   | 5.2 | 2.6 |
| G. W.   | 6.0*   | 7.6 | 5.6 |
| G. D.   | 9.9  | 5.9 | 4.0 |
| C. M.   | 10.4   | 5.9 | —   |
| Average | 9.2  | 6.2 | 4.1 |

\* We have not attempted to explain why this concentration was lower than that after 4 hours.

gm. After the first hour the concentration decreased, but a substantial amount was still present 8 hours after administration.

One hundred and twenty-four specimens of blood were obtained from 54 patients who were under continuous treatment with gantrosan. The patients were on a dosage regimen of 6 gm. initially, followed by 1 gm. every 4 hours. The blood concentrations ranged from 2.7 to 17.0 mg. per 100 cc., although 83% fell between 4 and 11 mg.

TABLE 1.—FREE BLOOD CONCENTRATIONS OF GANTROSAN AFTER THE ORAL ADMINISTRATION OF 6 GRAMS

| Subject | Concentration of Gantrosan (mg. per 100 cc.)<br>Hours after Administration |      |     |     |
|---------|--|------|-----|-----|
|         | 3  | 6    | 9   | 12  |
| J. S.   | 6.6  | 8.8  | 6.2 | 5.1 |
| J. H.   | 10.6   | 7.8  | 5.7 | 4.8 |
| T. C.   | 9.5  | 8.9  | 7.0 | 5.9 |
| H. W.   | 12.8   | 11.4 | 9.9 | 8.2 |
| L. J.   | 13.8   | 9.9  | —   | —   |
| Average | 10.7   | 9.4  | 7.2 | 6.0 |

centration of the drug was maintained for 6 hours, and that, although the concentrations fell off somewhat after this, the decrease was not striking. An average of 6 mg. per 100 cc. remained in

TABLE 3.—FREE BLOOD AND CEREBROSPINAL FLUID CONCENTRATIONS OF GANTROSAN

| Patient  | Concentration of Gantrosan (mg. per 100 cc.) |                     |
|----------|--|---------------------|
|          | Blood  | Cerebrospinal Fluid |
| C. H.    | 12.2   | 2.5                 |
| C. H.    | 12.2   | 3.4                 |
| H. K.    | 4.7  | 2.5                 |
| H. K.    | 4.6  | 1.6                 |
| G. W.    | 3.7  | 1.3                 |
| L. P.    | 8.4  | 3.4                 |
| D. M.    | 10.4   | 3.7                 |
| W. H.    | 8.9  | 2.9                 |
| Average* | 8.1  | 2.7                 |
| O. C.    | 13.8*  | 2.3**               |

\* Patients who had been on gantrosan therapy for 24 hours or more.

\*\* Specimens collected 2 hours after single oral dose of 6 gm.

The average blood concentration was 7.6 mg. per 100 cc. In one additional patient, who had renal insufficiency with azotemia, the blood gantrosan concentration reached 23.7 mg.

In Table 3 are shown the concentrations of free gantrosan present in specimens of blood and cerebrospinal fluid taken at the same time. The cerebrospinal fluid gantrosan concentration varied from 21 to 53% of the blood con-

monia were treated, with the exception of the rare patient who was admitted in *extremis* or with serious complications. As a result, only about 10% of the patients with typed pneumococcic pneumonia were over 50 years of age.

Among the 38 patients with typed pneumococcic pneumonia, 1 patient died, a 65 year old colored male with chronic bronchiectasis and uremia in addition to a bronchopneumonia. One

TABLE 4.—RESULTS OF TREATMENT WITH GANTROSAN

| Disease   | Number of Patients Treated | Successful | RESULTS<br>Unsuccessful | Died |
|---|----------------------------|------------|-------------------------|------|
| Pneumonia, Pneumococcic (typed)                               | 38                         | 36         | 1                       | 1    |
| Presumably pneumococcic*                                      | 41                         | 38         | 3                       |      |
| Secondary   | 7                          | 4          | 2                       | 1    |
| Klebsiella (Friedlander's)                                    | 1                          |            |                         | 1    |
| H. influenzae   | 1                          | 1          |                         |      |
| Hemolytic streptococcic                                       | 3                          | 2          | 1                       |      |
| Meningitis, Meningococcic                                     | 7                          | 6          | 1                       |      |
| Gonococcic  | 1                          | 1          |                         |      |
| Gonococcic Bacteremia   | 1                          | 1          |                         |      |
| Proteus endocarditis  | 1                          |            | 1                       |      |
| Bronchial asthma  | 3                          | 3          |                         |      |
| Acute bronchitis  | 3                          | 3          |                         |      |
| Acute exacerbation of chronic bronchitis<br>or bronchiectasis | 3                          | 3          |                         |      |
| Lung abscess (with penicillin)                                | 2                          | 1          | 1                       |      |
| Septic pulmonary infarct<br>(Beta-hemolytic streptococcus)    | 1                          |            | 1                       |      |
| Urinary tract infections.                                     |                            |            |                         |      |
| E. coli   | 8                          | 8          |                         |      |
| A. aerogenes  | 3                          | 3          |                         |      |
| Ps. aeruginosa  | 2                          | 2          |                         |      |
| Streptococcus gamma   | 1                          |            | 1                       |      |
| Etiological agent, undetermined                               | 15                         | 8          | 7                       |      |
| TOTAL   | 142                        | 120        | 19                      | 3    |

\* Primary pneumonia which resembled pneumococcic pneumonia clinically, but from which no pneumococcus was obtained.

centration. The average cerebrospinal fluid concentration for the 8 patients under continuous therapy was 1/3 of the average blood concentration.

**Results of Treatment.** Gantrosan was used by us in 142 patients. The results are shown in Table 4.

The first 15 patients with pneumonia were selected because the prognosis appeared favorable on the basis of age and the number of lobes involved. Later, all patients with bacterial pneu-

monia with typed pneumococcic pneumonia and 3 patients with untyped "atypical" pneumonia failed to respond to several days of gantrosan therapy and recovered later after the administration of penicillin. The patient with secondary pneumonia who died developed pneumonia following a gastric resection and received penicillin as well as gantrosan. Among the 36 patients with typed pneumococcic pneumonia who recovered after the use of the drug



alone, the temperature fell below 101° F. within 24 hours after the start of therapy in 15 patients (42%) and within 48 hours in 26 patients (72%). This compares favorably with the figures obtained by us for patients treated with other sulfonamides, namely 51% and 72% respectively<sup>2</sup>.

Nine (or 24%) of the patients with typed pneumococcic pneumonia had positive blood cultures when therapy was started. None of these patients died, although one was changed to penicillin therapy because he was not improving on the gantrosan regimen.

It will be noted from Table 1 that gantrosan was generally successful in the treatment of beta hemolytic and *H. influenzae* pneumonias. The one patient with a *Klebsiella* pneumonia who was treated unsuccessfully with gantrosan also had an acute nephritis with azotemia before treatment was started.

One patient with gonococcic meningitis and 6 with meningococcic meningitis were treated successfully. One patient with meningococcic meningitis has been classified in the unsuccessful group because his treatment was changed to penicillin after several days of only partial improvement on gantrosan therapy. He was an alcoholic who manifested delirium tremens during his disease and his course remained unchanged for several days after the shift to penicillin was made. He recovered ultimately.

The patient with gonococcic bacteremia recovered promptly on gantrosan therapy. Streptomycin was administered in addition to gantrosan to the patient with *Proteus* endocarditis but the combined therapy did not rid the blood stream of the organisms. The patient died 9 months later.

Various pulmonary infections other than pneumonia were treated and, in general, the responses were similar to those obtained with sulfadiazine or sulfamerazine. Thirty-nine patients with

urinary infections were treated. Among those in whom the etiologic agent was determined, the results were good with *E. coli*, *A. aerogenes* and *Pseudomonas aeruginosa* infections, and poor in the patient with a gamma streptococcic infection. Again, these results are similar to those obtained with other sulfonamides.

**Toxic Effects.** Hemoglobin determinations and leukocyte counts were made on alternate days on the majority of patients. Urinalyses were done on all patients 2 or 3 times a week, and in the case of 80 patients, careful urinalyses were done daily with special search for crystals and red blood cells.

Crystalluria was found in only 1 patient and then only in a single specimen. Careful search of subsequent specimens failed to reveal any crystals. One patient with meningitis developed gross hematuria during the second day of treatment. He had been receiving the drug intravenously up to that time. The hematuria lasted for 12 hours and then stopped in spite of the fact that gantrosan therapy had been continued. In none of the other patients was gross or microscopic hematuria found.

A maculopapular rash was observed in 1 patient, and fever, which was thought to be due to the drug, in 4 others.

Nausea without vomiting occurred in 4 female patients.

**Discussion.** If a new sulfonamide is to take a place alongside the sulfonamides which are of proven worth, it must be either superior therapeutically or less toxic than the sulfonamides which are already in use. Gantrosan apparently belongs to the latter class. Excluding nausea and simple crystalluria, only 6 patients experienced anything which could be called a toxic reaction. This percentage of toxic reactions (4.2%) compares favorably with those found by us for sulfadiazine (8.1%) and sulfamerazine (10.0%)<sup>2</sup>. It

is quite likely that a larger series of cases would reveal approximately the same incidence of all the toxic reactions, with the exception of the renal complications, as have been found following sulfadiazine and sulfamerazine therapy. The striking difference between gantrosan and the other sulfonamides (with the exception of sulfanilamide) is the infrequency of crystaluria and the almost complete absence of renal complications. As far as we know, no one else has observed gross hematuria as a complication of gantrosan therapy. Accordingly, it is quite possible that the hematuria was caused by something else in our patient. Inasmuch as it has been customary to regard any case of unexplained gross hematuria occurring during therapy with the other sulfonamides as a toxic effect of the drug, we have classified this case in that category. Since it may have been due to the precipitation of gantrosan in the urinary tract it should serve as a reminder to physicians using this drug that an adequate fluid output should be maintained here as in the case of the other sulfonamides.

As a therapeutic agent, gantrosan appears to be on a par with sulfadiazine and sulfamerazine. It is impossible to say this with certainty, however, since only a relatively small number of patients in each disease group were treated, and the sickest pneumonia patients were not treated. In the case of meningococcic meningitis it is likewise impossible to assay the value of a therapeutic

agent in the absence of an epidemic. One would welcome studies on large numbers of patients with this disease and with *Shigella* dysentery, the 2 major diseases in which sulfonamides are still the therapeutic agents of choice.

Our results with gantrosan in a few patients with urinary infections were similar to those obtained with other sulfonamides. Others<sup>1,6,7,8</sup> have reported moderate success in the treatment of urinary infections.

**Summary and Conclusions.** 1. One hundred and forty-two patients have been treated with gantrosan, a new sulfonamide which is more soluble at various levels of pH than the sulfonamides in general use.

2. Therapeutic results in various diseases, particularly pneumococcic pneumonia, meningococcic meningitis and various urinary infections caused by gram-negative rods, were similar to those observed following the use of sulfadiazine or sulfamerazine.

3. Urinary complications were limited to gross hematuria in 1 patient. Crystals were observed in the urine of 1 other patient. Dermatitis or fever attributed to the gantrosan was observed in 5 patients. Nausea occurred in 4 patients, vomiting in none.

4. Gantrosan is recommended for use when a sulfonamide is required in a patient where renal complications must be particularly guarded against.

We wish to thank Mr. Charles A. Toompas for the technical assistance he rendered.

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# THE TREATMENT OF GONORRHEAL ARTHRITIS WITH PENICILLIN

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This report is an evaluation of the effectiveness of penicillin in gonorrheal arthritis. It summarizes the experience on our wards for the past 3 years since this antibiotic has been employed.

**BASIS OF STUDY.** During this time 28 cases of gonorrheal arthritis received penicillin as the basic treatment as soon as the diagnosis was made. In 23 of these patients a presumptive diagnosis was based upon the clinical picture and course, together with the finding of a definite gonococcal infection in the genito-urinary tract. In the other cases 5 positive cultures were obtained from the joint

fluid. Aspiration of the joint was not attempted where the arthritis was limited to the small joints of the extremities or relatively inaccessible articulations like the shoulders. Effusions were aspirated in 10 cases and in 5 a positive culture was obtained.

The amount of treatment and the results for all 28 cases are presented in Table 1. The failures are reviewed in Table 2.

**RESULTS OF THERAPY IN PRE-PENICILLIN ERA.** The better to evaluate this still relatively new form of therapy, the results obtained in the past in the treatment of gonorrheal arthritis will be reviewed briefly. The methods employed fall into 4 major therapeutic groups: (1) Essentially non-specific and symptomatic therapy, (2) hyperthermy, (3) sulfonamides, and (4) the present use of penicillin.

Essentially non-specific methods consisted of sedation, bed rest, heat to joints, articular drainage, the parenteral use of various protein derivatives of the gonococcus, non-specific foreign protein therapy, and intravenous antiseptics. The simultaneous treatment of any genito-urinary focus was always advocated. Wehrbein<sup>25</sup> summarized the use of varying combinations of these methods in 610 cases and found none to have any marked advantage over the others. Classifying his cases into 4 grades of severity, with fever and joint pain as the criteria, he found that the average periods of hospitalization were roughly 7, 13, 27, and 36 days. In a group of 71 untreated cases the clinical

TABLE 1.—RESULTS IN 28 CASES OF GONORRHEAL ARTHRITIS

| Case | Diagnosis   | Penicillin received (millions of units) | Days Treated | Result           |
|------|-------------|---|--------------|------------------|
| 1.   | Presumptive | 1.6                                     | 8            | Cured            |
| 2.   | Proved      | 2.0                                     | 4            | Greatly Improved |
| 3.   | Proved      | 5.0                                     | 25           | Failure          |
| 4.   | Presumptive | 0.8                                     | 4            | Greatly Improved |
| 5.   | Presumptive | 0.5                                     | 3            | Greatly Improved |
| 6.   | Presumptive | 1.8                                     | 12           | Cured            |
| 7.   | Presumptive | 0.6                                     | 3            | Greatly Improved |
| 8.   | Presumptive | 4.0                                     | 14           | Cured            |
| 9.   | Presumptive | 1.0                                     | 5            | Greatly Improved |
| 10.  | Presumptive | 1.4                                     | 7            | Greatly Improved |
| 11.  | Presumptive | 9.3                                     | 18           | Failure          |
| 12.  | Presumptive | 4.3                                     | 30           | Greatly Improved |
| 13.  | Presumptive | 2.0                                     | 7            | Greatly Improved |
| 14.  | Presumptive | 2.3                                     | 8            | Greatly Improved |
| 15.  | Proved      | 1.8                                     | 6            | Cured            |
| 16.  | Presumptive | 3.2                                     | 10           | Greatly Improved |
| 17.  | Presumptive | 0.9                                     | 4            | Cured            |
| 18.  | Presumptive | 3.0                                     | 8            | Cured            |
| 19.  | Proved      | 7.0                                     | 18           | Cured            |
| 20.  | Presumptive | 2.5                                     | 8            | Greatly Improved |
| 21.  | Presumptive | 5.0                                     | 17           | Greatly Improved |
| 22.  | Presumptive | 4.0                                     | 10           | Failure          |
| 23.  | Presumptive | 1.6                                     | 10           | Cured            |
| 24.  | Presumptive | 3.0                                     | 10           | Failure          |
| 25.  | Presumptive | 1.6                                     | 10           | Failure          |
| 26.  | Presumptive | 3.5                                     | 12           | Greatly Improved |
| 27.  | Presumptive | 2.5                                     | 8            | Cured            |
| 28.  | Proved      | 0.5                                     | 6            | Greatly Improved |

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TABLE 2.—DATA ON CASES CLASSIFIED AS FAILURES

| Treatment   | Results   | Age<br>Sex<br>Race    | Diagnosis   | Joints Affected                               | Type of<br>Involvement | Duration Before<br>Treatment |
|---|---|-----------------------|-------------|---|------------------------|------------------------------|
| 5.0 million units<br>penicillin in 25 days.   | Temperature normal in 5 days. Acute signs<br>disappeared in 5 days. Flexion deformity<br>of knee present at discharge 64 days later.  | 25<br>negro<br>female | Proved      | Right knee                                    | Acute                  | 7 days                       |
| 9.2 million units<br>penicillin in 18 days.<br>(Stellate blocks for<br>complication of<br>reflex dystrophy)           | Temperature normal from onset. No change<br>in picture until stellate blocks started after<br>stopping penicillin. Residual weakness of<br>left grip and loss of flexion at discharge<br>60 days later. | 62<br>white<br>male   | Presumptive | Left wrist<br>3rd left<br>metacarpophalangeal | Acute                  | 21 days                      |
| 4.0 million units<br>penicillin in 10 days.<br>Sulfadiazine for<br>9 days later.                                      | Temperature elevated for first 3 weeks.<br>Slight improvement in knees but tender<br>and swollen on discharge 51 days later.  | 24<br>negro<br>male   | Presumptive | Both knees<br>Both wrists                     | Acute                  | 10 days                      |
| 3.0 million units<br>penicillin in 10 days.<br>4 knee instillations<br>of 50,000 units each.                          | Temperature normal on admission. Knee<br>remained swollen and tender during 35<br>days with little change.  | 13<br>negro<br>male   | Presumptive | Right knee                                    | Acute                  | 1 day                        |
| 1.6 million units<br>penicillin in 10 days.<br>Subsequent course of<br>sulfadiazine 7 days and<br>3 fever treatments. | Temperature remained elevated for 14<br>days. Minimal improvement in ankles<br>which remained tender.   | 37<br>white<br>male   | Presumptive | Both ankles                                   | Acute                  | 2 days                       |

course was similar. Treatment was concluded when the patient became ambulant and was able to leave the hospital, but no analysis in terms of joint function or follow-up was made. A more recent and detailed report by Spink and Keefer<sup>25</sup> concerned 70 cases given non-specific therapy. Twenty-six of these patients were treated by immobilization of the affected joints, attention to general nutritional measures, and the use of salicylates and opiates. This first group averaged 50 days in the hospital. Eighteen of the 26 were completely cured. There was persistent ankylosis in 4 patients and residual stiffness in the affected joints of the remaining 4. The second group of 44 patients received the same basic treatment but, in addition, aspiration or open lavage of the joints was done for purulent effusions. Of these 44, only 17 showed complete joint recovery, while the remainder were left with varying degrees of ankylosis or stiffness.

Other investigators have stated that in the pre-specific era gonorrheal arthritis led to some degree of permanent disability in 25% of the cases.<sup>1</sup>

The period of fever therapy began in the early 1930's and marked a great improvement in results. A comprehensive summary and comparison of the outcome of hyperthermy and the previous non-specific therapy in the same hospital were given by Schnabel and Fetter<sup>23</sup>. In 2 series of 93 cases each, 54 were completely cured by fever as against only 5 cures with non-specific methods. The criteria of cure were the complete restoration of joint function and the disappearance of gonococci from any preexistent focus.

Summarizing the status of fever therapy in the treatment of gonorrheal arthritis, Hench<sup>12</sup> stated that, if early and adequate treatment is given, patients have an 80% chance of being cured with an additional 10% chance of being greatly relieved. In these acute cases

the treatment was regarded by him as specific and the diagnosis open to doubt if no response occurred. In cases of over 6 weeks' duration the proportions of cure and great relief dropped 30% and 35% respectively, with ankylosis and stiffness as more likely complications.

Following the introduction of the sulfonamides the use of fever became relatively infrequent. Owing to the technical difficulties of administration and an occasional severe complication, hyperthermy became reserved for those cases resistant to the sulfonamides<sup>24</sup>.

It soon became evident that the results from using sulfonamides were at least equal to those from fever therapy. Coggleshall and Bauer<sup>3</sup> observed that 11 of 18 cases showed striking clinical improvement in 48 to 72 hours and that the end results in all cases were more satisfactory and took place in a shorter time than occurred with other forms of therapy. Keefer and Rantz<sup>17</sup> reported 14 carefully studied cases in which return of joint function was one of the criteria of cure. Twelve of these 14 were cured. Hospital stays, however, ranged from 16 to 90 days and the authors noted that "in spite of the sterilization of the synovial fluid within a relatively short time, the damage to the synovial membrane may require a long period for recovery." Other authors reported similar results<sup>2,13</sup>.

Within the last few years it has been widely observed that cure rates in genito-urinary gonorrhea treated with sulfonamides have declined strikingly<sup>11,19</sup>. We have not found any similar reports in the treatment of gonorrheal arthritis.

**PENICILLIN IN GONORRHEAL ARTHRITIS.** The first report of the use of penicillin in gonorrheal arthritis appeared in 1943<sup>16</sup>. Most data have come from the Armed Forces and consist of large numbers of cases of genito-urinary gonorrhea resistant to sulfonamides treated

later with penicillin. Gonorrheal arthritis is mentioned as one of the many complications without further details<sup>5,11,19,21,22</sup>. Tabulation of those series which give the incidence of complications shows gonorrheal arthritis occurring in less than 1% of the total number of sulfonamide resistant cases. This indicates that the actual incidence of arthritis as a complication of gonorrhea was much less than the 1 to 3% which was thought to be the average before the era of specific treatment. Hench and Boland<sup>14</sup>, reviewing their experience at an Army Rheumatism Center, stated that proved gonorrheal arthritis was very rare. They believed that the majority of the cases referred to them were really suffering from rheumatoid arthritis precipitated or aggravated by the gonorrheal infection. The later clinical course of their patients led them to make this diagnosis.

The most comprehensive series to date has been that of Hirsch, Feffer, and Dowling<sup>15</sup>. They reported 17 cases of proved gonorrheal arthritis. Of these, 15 were acute and of less than one month's duration. The first 7 of these acute cases received 200,000 to 2,400,000 units of penicillin in 8 to 30 hours. In this group the genito-urinary focus cleared promptly, but there was no improvement in the arthritis. The authors state that "all subsequently finally recovered on symptomatic measures, sulfonamides or fever therapy". The next group of 8 acute cases received 1,000,000 to 2,000,000 units of penicillin over a period of 5 to 10 days. All showed complete recovery of joint function. The authors believed that the prolongation of the treatment in the second group of acute cases accounted for the good results. Penicillin has been used, but its place has not been established yet in keratosis blennorrhagica, which some regard as a complication of gonorrheal arthritis. There is, however, increasing evidence that the cutaneous

features may be a symptom of Reiter's syndrome<sup>10</sup>.

**Analysis of Results in Our Series.** In each of our 28 cases the extra-articular focus of infection, such as urethritis or cervicitis, was eliminated promptly by the use of penicillin, and subsequent smears or cultures remained negative during their hospital stay. Since this factor remained constant, we could assume that the infecting organism had been destroyed, in each patient. We evaluated the results according to the response of the arthritis. No special complications such as iritis or tenovaginitis occurred. The average duration before hospitalization was 7 days.

Cured patients were those with completely restored joints. Greatly improved were those in which the following were observed: (1) fever, if present, quickly subsided; (2) signs of acute joint inflammation such as pain, swelling, redness and heat promptly resolved or were markedly alleviated; and (3) the residual joint involvement consisted only of slightly limited motion or tenderness. Not improved, or failures, were those patients who showed residual deformity or in whom no apparent change in the joint involvement was noted during the course of penicillin therapy.

Using these criteria, 8 of our patients were cured, 15 were greatly improved, and 5 were not improved.

Although 28 cases provide too small a series for statistical analysis, the results in 23 of the 28 patients showed a trend toward therapeutic effectiveness at least equivalent to, or greater than, the outcome from sulfonamides or fever therapy and far superior to the results in the non-specific era without any of their complications.

**Discussion and Deductions.** The satisfactory results, as well as the failures, of the use of penicillin must be surveyed in the light of the therapeutic goals in the treatment of gonorrheal as

well as any other type of arthritis. The objectives are: first, arrest of the specific process; second, palliation by symptomatic relief and constitutional improvement; and third, prevention and correction of deformity.

It seems certain that penicillin usually can be expected to arrest the infection. In every one of these 28 cases, including the 5 regarded as failures, the fever promptly subsided, all pain and acute swelling of joints disappeared, and there were no instances of progression of signs, newly inflamed joints or reactivation of the initial focus after penicillin was started. Although cultures of joint fluid were not done after treatment was instituted, it is a likely assumption that in every one of these cases the penicillin produced a bacteriologic cure.

Such a deduction is supported by other evidence. In a large survey series Finland and Meads<sup>8</sup> concluded that proof of *in vivo* fastness of the gonococcus had not been reported. It had been shown that repeated subculturing of the gonococcus *in vitro* could produce temporary penicillin fastness<sup>20</sup>. Since then, however, Franks<sup>9</sup> has described 4 cases of penicillin-resistant gonococcal urethritis which responded to fever therapy. Others have employed fever therapy in combination with penicillin as a routine<sup>6</sup>.

Our experience indicates that the bacteriologic cure that can be effected by penicillin does not eliminate the need for attaining the two other goals in the treatment of any form of arthritis, symptomatic relief and the prevention or correction of deformity. Thus in 10 of the last 12 cases followed personally by us, residual joint involvement had to be treated for an average period of 3 weeks even though the penicillin eliminated active gonococcal infection. The joint signs and symptoms in these cases were due to thickened, persistently inflamed synovial

membranes, inflamed extra-articular structures, or damaged cartilage surfaces. The therapeutic problem then becomes similar to that seen in other chronic arthritides, where the proper use of immobilization, movement, the various physiotherapeutic modalities and, finally, corrective orthopedic procedures are necessary for satisfactory results.

The advent of the antibiotics, with their rapid destruction of the etiologic organism, probably requires a revision of methods of management in those infections amenable to the new therapeutic agents. The principles of rest and immobilization of infected joints, sometimes for long periods, to assure fixation in optimum positions, served their purpose when specific infections frequently and inevitably threatened serious articular damage and an ankylosed joint. When arthritis is due to an organism susceptible to antibiotics, the older methods probably must be modified now for the best results. More attention must be given to the judicious use of physical therapy and exercise in increasing amounts as soon as the infection is under control and within the range of the patient's tolerance. The adequate use of posterior resting splints, rather than prolonged immobilization, seems more suitable. The discreet application of the foregoing measures to supplement the antibiotics would constitute a proper reorientation in the management of these disorders now that a dependable specific measure is available to overcome the infection.

The following brief case histories illustrate some of these points.

Case Abstracts CASE 1 H M, a 22 year old negro male, gave a history of sexual intercourse followed by a purulent discharge in 2 days. Several days later both shoulders became painful but soon subsided, and the left wrist became markedly painful, swollen, hot and tender, with no motion possible. Temperature on admission was 101° F. Urthral culture was positive. Roentgen-ray films of

the wrist were negative, excepting soft tissue swelling. The left wrist was immobilized in a bass-wood splint, and active motion instituted twice daily. There was great relief of pain as soon as the wrist was immobilized. Penicillin (30,000 units every 3 hrs.) was started. Temperature was normal in 2 days. Swelling and acute pain left the wrist in 24 hours. All tenderness was gone in 6 days, and no limitation of motion remained.

This case represents a bacteriologic and functional cure. Penicillin was started 48 hours after the onset of the arthritis and articular damage was probably minimal.

CASE 2. M. B., a 19 year old negress, was admitted for a painful shoulder and a painful, swollen knee of 7 days' duration. Subsequently, there was involvement of the left sternoclavicular joint. Cervical and knee joint fluid cultures were positive for gonococcus. The initial temperature was 101° F. Penicillin (20,000 units every 3 hrs.) was started on the 9th day, and continued for a total of 2,000,000 units. The temperature fell to normal, and the swelling and pain present both in the knee and the sternoclavicular joint largely subsided in 3 days. Residual stiffness and pain, together with a slight fullness of the joint, remained in the left knee at the time of discharge, 22 days after the onset of therapy. The patient received daily short-wave diathermy treatments after the subsidence of the acute symptoms. Roentgen-ray films of the knees were negative in this case.

This represents a greatly improved case. Bacteriologic cure was effected, but residual stiffness and pain remained. These probably were due to synovial thickening and damage prior to the beginning of penicillin therapy.

CASE 3. M. C., a 25 year old negress, entered with a history of a painful swollen knee of 3 weeks' duration. The patient was married, and there was no history of urethritis or cervicitis, but cervical cultures were positive for gonococci. Fluid from the knee was purulent and yielded a positive culture of gonococci. Roentgenograms showed evidence of articular destruction. Penicillin therapy was started (30,000 units every 3 hrs.). The initial temperature of 101° F fell to normal in 2 days, the patient felt much improved, and the pain and swelling of the knee subsided almost completely in 5 days. It was noted at this time, however, that the knee could only be extended to 155 and remained

quite tender. A circular cast was then applied with the intention of subsequently wedging it. When first seen by us, this cast had been on for 10 days. The cast was removed and it was found that the knee was "frozen". Penicillin had been continued throughout this period. Daily physiotherapeutic treatment was instituted, but after 3 months this patient still had a contracture of the knee causing her to limp.

This case is one of the 5 failures. The residual changes as well as the poor functional result cannot be attributed to lack of efficiency of the penicillin. The outcome probably would have been influenced considerably by the use of posterior molded splints with at least a minimum of daily active or passive motion from the start. In that way the initial contractures might have been avoided. Furthermore, since Roentgen-ray films already showed articular damage, there probably was especially good reason here to avoid prolonged immobilization.

**Summary.** 1. Twenty-eight cases of gonorrheal arthritis treated with penicillin are reported. Of these, 23 were regarded as cured or greatly improved, 5 as failures.

2. Penicillin effected a bacteriologic cure in every patient, according to the clinical course.

3. The over-all results, however, depend on other factors, too. Measures to preserve joint function and in that way to prevent residual disability, or to overcome impending contractures, must be instituted without delay.

4. The trend of results, both for bacteriologic and functional cure, indicates a therapeutic effectiveness at least equivalent, perhaps superior, to previous methods of treatment.

5. Earlier judicious use of joint motion and physiotherapeutic modalities as a supplement to penicillin therapy, seems to be indicated in the management of this infectious arthritis in the new era of antibiotics.

We are indebted to Dr. John Deitrick, Dr. D. J. Richards, Jr., and Dr. W. S. Tillett for cases from their medical divisions included here.

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# INEFFICACY OF PROPHYLACTIC STREPTOMYCIN IN AN OUTBREAK OF SALMONELLA GASTRO-ENTERITIS\*

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THERE is, at present, little published evidence of the efficacy of streptomycin therapy in salmonella infections. As part of the investigative program of the National Research Council in which streptomycin was used to treat various infections, 26 cases caused by salmonella were studied<sup>1</sup>. The results of therapy were thought to be poor. In a review by Pulaski and Amspacher<sup>2</sup> of the experience of the U. S. Army with streptomycin in the treatment of certain infections of intestinal origin 10 cases of salmonella infections have been reported. They regarded the results of therapy in their cases as favorable, but found them difficult to evaluate since this is often a self-limiting disease.

Because relatively few cases of salmonella infection treated with streptomycin have been reported and since the results of therapy are inconclusive<sup>2,4</sup>, we believe there is value in reporting our rather unique experience of being able to follow several patients who were receiving streptomycin at the time the infection occurred and to compare their course with that of patients infected with the same strain of organisms but who did not receive streptomycin.

An outbreak of acute gastro-enteritis occurred among the patients on the Tuberculosis Unit of the University Hospital. This outbreak was found to be limited to those individuals who received a certain feeding of a high carbohydrate and high protein formula, an enriched milk drink used for interval nourishment in patients who are underweight. Six of the persons with the digestive upset were patients on the unit, and 2 non-patients who drank the formula developed similar illnesses clinically. We were unable to follow the 2 non-patients. Organisms, identified by cultural and serological methods as *Salmonella schottmülleri*, were isolated from the suspected formula and from the stools of the 6 tuberculous patients. All 6 patients received for their salmonella infection similar treatment, consisting of strict bed rest, intravenous fluids to correct their dehydration, and sulfadiazine. The sulfadiazine was given in the dose of 2.0 gm. stat, then 1 gm. every 4 hours for 3 to 6 days. In addition, 2 of the patients who developed the enteric infection were receiving intramuscular streptomycin as part of their therapy for recent pulmonary tuberculosis at the time of the outbreak.

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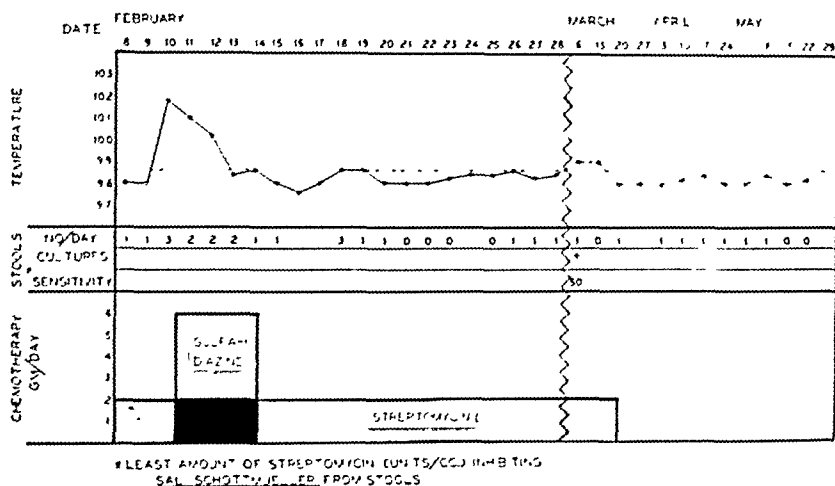


FIG. 1.—Chart of J. S., 604584, a 24-year old white woman, with bilateral far advanced pulmonary tuberculosis who was being treated with strict bed rest and streptomycin (begun on 12-17-46). On the night of 2-9-47 she was awakened from her sleep by severe abdominal cramps and backache. This was followed by malaise, nausea and vomiting. On the following morning her stools were loose and watery. Her symptoms slowly subsided over a period of 3 weeks. She lost only  $\frac{1}{2}$  pound of weight during this period.

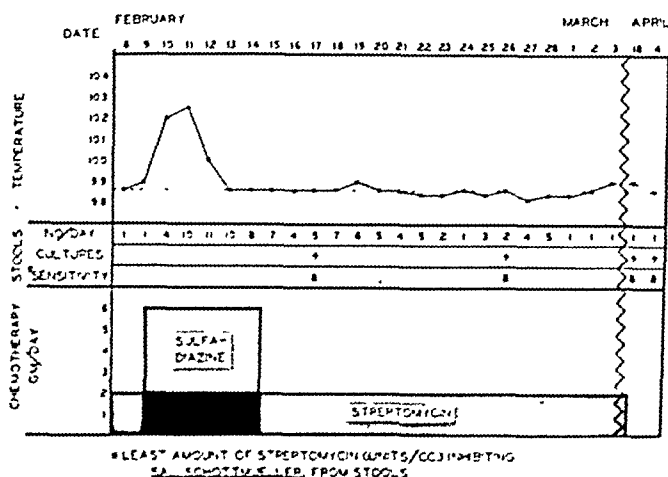


FIG. 2.—Chart of A. M., 552955, a 30-year old white woman, hospitalized because of moderately advanced pulmonary tuberculosis and tuberculous enterocolitis. On December 16, 1946 she was started on streptomycin for her intestinal tuberculosis. There was excellent symptomatic improvement and stools became normal in number and consistency. She gained 23 pounds in weight (109 to 132). During the night of 2-9-47 she had loose stools without other symptoms. On 2-11-47 she developed nausea, vomiting, chills, fever, abdominal cramps and had 10 watery blood-tinged stools. The vomiting stopped the following day and the nausea in 5 days. The abdominal cramps continued until 2-19-47. During this period there was an 11-pound weight loss. Her stool cultures were still positive at the time of her transfer to a sanatorium on 4-5-47.

the dosage given being 0.4 gm. every 4 hours from 8:00 a.m. until midnight, totaling 2 gm. a day. Routine streptomycin serum level determinations during this episode on the patient described in Fig. 1 showed a peak level (1 hour after the injection) of 32 mcg. per cc. and a low level of 16 mcg. per cc. just prior to the next injection. These levels are similar to those obtained at other times during her course of streptomycin. The second patient, Fig. 2, had a peak streptomycin serum level of 19.5 mcg. per cc. during her salmonella infection and had similar

patients at some time during the course of the infection.\* Cultures were not obtained on the other 2 affected individuals. Five of the 6 patients continued to yield positive cultures of *Sal. schottmülleri* for long periods after the subsidence of subjective symptoms.

All of the strains were tested for sensitivity to streptomycin but none to sulfadiazine. The organisms isolated from the formula and from the stools of patients who did not receive streptomycin were all inhibited by 8 mcg. per cc. of streptomycin but not by 4 mcg. per cc. This remained constant through-

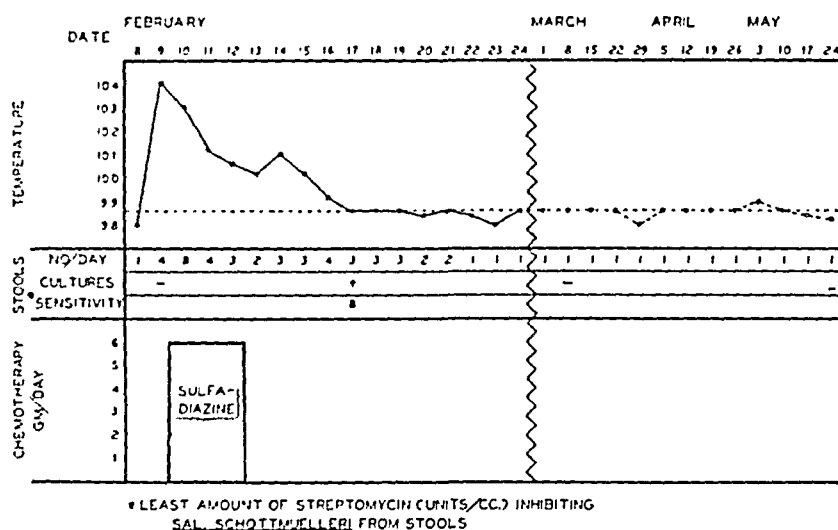


FIG. 3.—Chart of J. R., 534535, a 19-year old white woman, with moderately advanced pulmonary tuberculosis, being treated with strict bed rest and right pneumothorax. Severe abdominal cramps and nausea with vomiting accompanied the fever and diarrhea on 2-9-47. These symptoms subsided over a period of 3 days. There was a 6-pound weight loss during this period.

levels at other times. Four of the patients not receiving streptomycin at the time of the salmonella outbreak had comparable clinical courses to those of the 2 patients receiving the antibiotic. Fig. 3, describing the course of the disease in one of these 4 patients, is included for comparison. The course was similar in all 4 patients.

**Bacteriology.** *Sal. schottmülleri* was isolated from the stools of all 6 of the

out the patients' course (See Fig. 3). Of the 2 patients who were receiving streptomycin parenterally at the time of the outbreak, the organisms persisted in the stools of one (Fig. 2) for several months and retained the original sensitivity (8 mcg. per cc.) as long as observed. The only positive culture from the other patient (Fig. 1) was obtained 1 month after the onset, at which time the organisms were inhib-

\* Isolation and identification of the causative organisms was performed in the Bacteriology Laboratory of the University Hospital, Ann Arbor, Michigan.

ited by 50 but not by 20 mcg. per cc. of streptomycin. A third patient (chart not shown) was started on a course of streptomycin for her pulmonary tuberculosis after the subsidence of symptoms from her gastro-enteritis. A culture obtained before the institution of streptomycin therapy was inhibited by 8 mcg. per cc.; after 10 days' administration of the drug the organisms were inhibited by 100 but not by 50 mcg. per cc.

**Comment.** There was no demonstrable difference in the course of the disease in the patients who received streptomycin as compared with those who did not. Tissue invasion by the infecting organisms occurred in spite of blood levels of streptomycin well above those which inhibited the growth of the organisms *in vitro*. We appreci-

ate the paucity of our knowledge concerning the relationship between *in vitro* and *in vivo* sensitivity of organisms to antibiotics.

**Summary and Conclusions.** 1. An outbreak from a known single source of 8 cases of *Sal. schottmülleri* gastro-enteritis is described.

2. Two patients receiving parenteral streptomycin therapy at the time the infection occurred had courses comparable to those of patients not receiving the antibiotic, although their streptomycin serum levels were well above the *in vitro* sensitivity of the causative organisms.

3. No correlation can be found between the failure of streptomycin therapy and the development of streptomycin resistance by the organisms.

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# MULTIPLE MYELOMA ASSOCIATED WITH POLYCYTHEMIA REPORT OF FOUR CASES\*

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THE simultaneous development of myeloma and polycythemia vera in one patient is of interest for a number of reasons. They both chiefly involve the bone marrow. Their etiologies are unknown, and their simultaneous appearance is rare. In fact, myeloma has commonly been associated with anemia. A review of the literature reveals 3 reports of polycythemia vera associated with a possible myeloma. In none of these cases has the diagnosis of myeloma been positively established, if one uses the strict criteria of identifying predominantly myeloma or plasma-like cells in the tumor or their increase in the bone marrow. These criteria are in accordance with the most recent publications on myeloma to be mentioned later.

Pribram<sup>13</sup> described a patient with polycythemia, Bence-Jones proteinuria and the appearance, by Roentgen ray examination, of tumors in the sternum and ribs. As Bence-Jones proteinuria has been found in patients with bone marrow disease other than myeloma<sup>3,8</sup>, and no biopsy or necropsy was obtained in this case, the diagnosis of myeloma was not definitely established.

Perla and Biller<sup>12</sup> reported the case of a 30 year old patient with polycythemia vera. Thirteen years later, after benzene and Roentgen ray therapy, the red cell count was 3.5 million. The patient died 2½ years later with anemia,

white cell count of 3,100, 22% myeloblasts in the peripheral blood, urine negative for Bence-Jones protein, enlarged liver and spleen, and multiple soft tissue masses in the head, sternum, abdomen and groin. Autopsy revealed a tumor described as a hemoblastic or stem cell sarcoma of a primitive red cell type showing diffuse invasion. The tumor masses and bone marrow were similar in appearance with sheets of primitive cells surrounded by pro-erythrocytes, erythroblasts and normoblasts. The pathological picture of this case resembles that of cases described by Ribbert<sup>14</sup>, Smith<sup>17</sup>, and Taylor<sup>18</sup> as multiple myeloma of the erythroblastic type. These cases are of further interest because they were regarded as multiple myeloma although few, if any, myeloma or plasma cells could be found in sections of the tumor. However, recent articles indicate that myeloma cells may be identified more positively and readily in smear preparations than in histological cut sections<sup>3,4,6,7,8,10,15,20</sup>. This difference is partly attributed to the marked variations in morphology of the myeloma cell which may at times closely resemble other cell types such as the erythroblast. Pertinent is the case described by Taylor which revealed 23% plasma cells in a bone marrow smear, while in the histological section of the tumor obtained shortly afterwards at autopsy only a few plas-

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ma cells could be recognized. The case described by Perla and Biller could be called a myeloma of the erythroblastic or possibly the hemoblastic type under the system of classification<sup>1</sup> of myeloma formerly in vogue before the widespread use of smear preparations from sternal aspiration. However, the absence of recognizable myeloma cells in this case makes the definite diagnosis of myeloma uncertain.

The third case, reported by Arnold<sup>2</sup>, was a patient who had polycythemia for 13 years prior to death following splenectomy performed for splenic infarction. At autopsy, soft, myeloma-like nodules were found in the marrow of both femurs. Histologically, these nodules appeared to be due to hemorrhage and connective tissue reaction, not myeloma.

Since Bence-Jones proteinuria is often associated with myeloma, it is of interest to note that one other case of Bence-Jones proteinuria in polycythemia vera, besides that of Pribram, has been described. This case, reported by Tsuji<sup>10</sup>, had no other clinical evidence to suggest the presence of myeloma.

Four cases of definite myeloma associated with polycythemia are reported here.

**Report of Cases.** CASE 1. G. K., a 59 year old man, was seen in October, 1942, with a 1 year history of fatigue, dizziness, headaches, occasional blurring of vision and marked flushing of the face. Past history was non-contributory.

Physical examination revealed a round-bodied male with a ruddy complexion. Blood pressure was 140 mm. mercury systolic and 90 diastolic. Skin was diffusely covered with small blood blisters. Retinal veins were engorged. Liver and spleen were not enlarged.

Peripheral blood showed hemoglobin 17.3 gm. per 100 cc., red cell count 5.55 million, white cell count 19,800 with a normal differential count, platelet count 440,000, and hematocrit 60%. The urine was negative.

**Course.** A possible diagnosis of polycythemia was made and 3 phlebotomies of 500 cc. each brought the hematocrit down to 47% with some symptomatic relief. The patient was

placed on a maintenance dose of phenylhydrazine but his former symptoms returned in a few weeks.

From February to September, 1943, he was treated with radioactive phosphorus and received a total of 35.33 millicuries in 9 doses. The red cell count varied between 5.8 to 7.48 million. The patient never showed any definite symptomatic improvement. Fatigue and headache continued to be the chief complaints.

In the summer of 1944, the patient developed pain in the lower dorsal spine radiating to the right lower chest posteriorly. The headaches and dizziness improved but the marked fatigue and weakness persisted.

In November, 1944, a roentgenogram revealed a lesion involving the ninth dorsal vertebra. At that time, the hemoglobin was 14.8 gm. per 100 cc., red cell count 4.14 million, white cell count 12,900 and hematocrit 46%.

The patient was next seen January 16, 1945, at which time the back pain was more severe and characteristic of root pain. The blood count was essentially unchanged. A roentgenogram showed a slight but definite increase in the destructive lesion of the ninth dorsal vertebra. Blood calcium, phosphorus and alkaline phosphatase were normal. Erythrocyte sedimentation rate was 15 mm. after 1 hour.

In March, 1945, the pains in the spine and chest increased. The patient developed paresthesias, numbness and tingling of the toes and fingers. Roentgenogram showed further increase of the lesion in the ninth dorsal vertebra and a pathological fracture at that site. He developed ataxia of the lower extremities and progressive weakness. Lumbar punctures revealed an increased globulin in the spinal fluid.

The patient died on September 9, 1945. Post mortem revealed a destructive tumor of the seventh, eighth and ninth vertebrae. Microscopic examination of the tumor showed a predominance of the plasma cells to establish the diagnosis of myeloma. It is impossible to state whether or not there was an increase of plasma cells in the sternal marrow section. Although only a single myeloma lesion was found at autopsy, it is very likely that there were multiple lesions. A review of the roentgenograms revealed osteoclastic lesions in the region of the left acetabulum, upper portion of the left femur, wings of the ilia and the sacrum. These areas were not examined at the post mortem. Unfortunately, since the patient was taken care of elsewhere during the last 2 years of his life, the urine was never tested for the presence of Bence-Jones protein and a sternal puncture was never done.

*Summary.* The patient had symptoms and blood picture consistent with a diagnosis of polycythemia vera. There was no symptomatic improvement after treatment with radioactive phosphorus, although the red cell count did fall to normal levels after the administration of 35.33 millicuries over a 7 month period. Two years after the discovery of polycythemia, the patient developed symptoms from a destructive lesion of the ninth dorsal vertebra. He died one year later and at necropsy the lesion was found to be a myeloma composed predominantly of plasma cells.

CASE 2. E. B., a 50 year old housewife from Mexico City, was seen in January, 1948. Her chief complaints were diffuse, constant pains in the arms and legs for 6 months.

*History.* In November, 1947, at Mexico City, she was found to have a red cell count of 6.8 million and a hemoglobin of 20.3 gm. per 100 cc. Three weeks later her red cell count was 8.77 million; and, after spending 2½ weeks at sea level, it was 7.05 million with hematocrits of 61 and 56% respectively. At that time, the patient was found to have a Bence-Jones proteinuria. Laboratory tests revealed an impaired renal function with a low fixed specific gravity. Blood proteins showed no abnormality. Erythrocyte sedimentation rate was 29 mm. after one hour (corrected). There was some symptomatic improvement after a phlebotomy of 325 cc.

Past history revealed meningitis in childhood, double pneumonia at the age of 24 years, and possible nephritis at 44 years. She had been a known diabetic for 15 years and had been well controlled by diet and insulin for 7 years.

When seen at Berkeley, which is at sea level, the patient complained of malaise and headache. She had a temperature of 102.4° F. and was found to have a bilateral pneumonia which responded to penicillin.

On *physical examination*, the blood pressure was 150 systolic and 70 diastolic. Lungs revealed a slight emphysema with bilateral sticky basal rales. Liver and spleen were not palpable and there was no lymphadenopathy.

*Blood studies* revealed a red cell count of 5.2 million, hemoglobin of 14.5 gm. per 100 cc., platelet count of 350,000, and white cell count of 10,700 to 12,300 (1% polys non-segmented, 60% polys segmented, 2% eosinophils, 36% lymphocytes, 2% monocytes). There were 1 to 2 nucleated red cells per 100 white cells. Urine was positive for albumin and Bence-Jones protein. Roentgenograms of the skull and thorax revealed no bone lesions. Bone marrow obtained by sternal puncture revealed:

|                                  |         |
|----------------------------------|---------|
| Total count . . . . .            | 500,000 |
| Myeloblasts . . . . .            | 1.2%    |
| Pre-myelocytes, eos. . . . .     | 4.4%    |
| Myelocytes, neut. . . . .        | 11.8%   |
| Myelocytes, eos. . . . .         | 0.2%    |
| Neutrophils, juv. . . . .        | 16.2%   |
| Neutrophils, stabs . . . . .     | 20.4%   |
| Neutrophils, segmented . . . . . | 16.4%   |
| Eosinophils . . . . .            | 2.0%    |
| Basophils . . . . .              | 0.8%    |
| Lymphocytes . . . . .            | 1.2%    |
| Plasma Cells . . . . .           | 9.6%    |
| Plasmablasts . . . . .           | 0.6%    |
| Megaloblasts . . . . .           | 1.2%    |
| Erythroblasts . . . . .          | 2.4%    |
| Pro-normoblasts . . . . .        | 2.4%    |
| Normoblasts . . . . .            | 8.6%    |
| Megakaryocytes . . . . .         | 0.6%    |

The 9.6% plasma cells established the definite presence of myeloma, which accounts for the Bence-Jones proteinuria.

Patient's status was essentially unchanged on September 20, 1948. In the high altitude of Mexico City, she has symptoms of dyspnea and pains in the extremities, while at low altitudes she is asymptomatic. The polycythemia in this case was thought to be related to a combination of high altitude, chronic bronchitis, emphysema and myeloma.

*Summary.* This patient came from a high altitude locality where she was found to have a polycythemia which disappeared when she was at sea level. Her polycythemia was also partly secondary to a chronic bronchitis and emphysema. She complained of pains in her arms and legs and was found to have a Bence-Jones proteinuria. The diagnosis of myeloma was established by the discovery of 9.6% plasma cells in aspirated sternal marrow. She has been relatively asymptomatic almost one year after the discovery of the polycythemia and myeloma.

CASE 3. B.C., a 65 year old woman, was referred to us in January, 1949, with the diagnosis of polycythemia vera. She had an 8 month history of progressive weakness and paresthesias of the arms and legs, with unsteady gait. For about 2 years, there was increased redness of the face, most marked in the past 6 months, and marked reddish cyanosis of the hands and feet. She had been on an elimination diet for the past 2 years for a dry "allergic" cough. 3 months previously, she had an episode of marked dizziness. At that time, there was enlargement of the liver and spleen, 5.21 million red blood cells and a hematocrit of 53%.

*Physical examination* revealed a small woman with a florid complexion and slight cyanosis of the hands and feet. Blood pressure



was 180 systolic and 90 diastolic. The heart was not enlarged, the lungs were clear, the liver was palpable 11 cm. below the costal margin and the spleen was not palpably enlarged. There was no lymphadenopathy. Neurological examination revealed absent deep reflexes and vibratory sense of the lower extremities with slight muscle weakness.

Blood studies revealed a red cell count of 4.95 million, hemoglobin 17.5 gm. per 100 cc., white cell count 15,000 with a normal differential and platelet count of 380,000. The hematocrit was 53 and 54% on 2 occasions. The possibility of polycythemia vera leading to multiple thromboses of the vessels of the spinal cord was considered, but sternal puncture seemed indicated.

Bone marrow obtained by sternal puncture revealed:

|                              |       |
|------------------------------|-------|
| Myeloblasts .....            | 1.2%  |
| Pre-myelocytes .....         | 2.4%  |
| Myelocytes, neut. ....       | 13.6% |
| Myelocytes, eos. ....        | 1.4%  |
| Myelocytes, bas. ....        | 0.2%  |
| Neutrophils, juv. ....       | 4.0%  |
| Neutrophils, stab. ....      | 13.0% |
| Neutrophils, segmented ..... | 14.0% |
| Eosinophils .....            | 1.4%  |
| Basophils .....              | 0.2%  |
| Lymphocytes .....            | 4.2%  |
| Plasma Cells .....           | 12.8% |
| Plasma Cells, 4 nuclei ..... | 0.2%  |
| Plasma Cells, 2 nuclei ..... | 0.4%  |
| Megaloblasts .....           | 0.8%  |
| Erythroblasts .....          | 3.0%  |
| Normoblasts .....            | 24.6% |
| Megakaryocytes .....         | 1.2%  |

Thus, the unexpected diagnosis of multiple myeloma seemed established, providing an explanation for the neurological symptoms and signs. Bone marrow obtained from the iliac crest showed a similar picture.

Urine was negative for Bence-Jones protein but showed a trace of albumin. Roentgen ray examinations revealed areas of rarefaction in the region of the right acetabulum and in the right 5th rib. There was considerable narrowing of the intervertebral space between the 4th and 5th lumbar vertebrae suggestive of a disc herniation. Blood proteins revealed an albumin of 3.8 and globulin of 3.0 grams per 100 cc. Alkaline phosphatase was 2 Bodansky units. Blood coagulation studies revealed a clot retraction rate, obtained by electric resistance measurement, of 9.7 ohm-cm. per minute and heparin clotting time of 21 minutes. Both values are in the normal range.

**Summary.** This patient had an 8 month history suggestive of polycythemia vera. Although the patient did not have a significantly elevated red cell count when seen by us, her elevated hematocrit, history and florid appearance were strongly indicative of polycythemia vera. Bone marrow revealed 13% plasma cells and Roentgen ray examination showed 2 areas of bone rarefaction. The diagnosis of multiple myeloma was thus established and the patient was placed under treatment with Roentgen rays to the spine and radioactive phosphorus intravenously.

**CASE 4.** H.D., a 56 year old man, was seen by Dr. Nathan Rosenthal in March, 1946, with the complaint of a pain in the left upper quadrant and in the left shoulder on inspiration. In 1943, his friends noted his unusually red complexion. 6 months previously, a cholecystectomy and appendectomy were performed and his blood was noted to be "rich".

**Physical examination** revealed a man with a very florid complexion. Liver was palpable 2 finger breadths below the costal margin and the spleen was enlarged to the iliac crest.

**Blood examination** revealed a red count of 7.3 million, hemoglobin 145%, hematocrit 73%, white cell count 18,750 with 83% segmented neutrophils and platelets 500,000.

**Course.** The patient disappeared and no follow-up was possible. Apparently, he was treated with venesections in another city until December, 1947, when he complained of nausea, vomiting, dizziness and weakness of one week's duration. He did not appear acutely ill. His face was hyperemic and the spleen was palpable 3 finger breadths below the costal margin. The red cell count was 4.75 million and the blood non-protein nitrogen was markedly elevated. The blood proteins showed an albumin 2.5 and globulin 8.1 gm. per 100 cc. The patient went progressively downhill and died 2½ weeks later.

**Necropsy** revealed numerous plasma cells in the bone marrow of the sternum and the interstitial tissue of the kidneys containing focal accumulations of plasma cells.

**Summary.** This patient had known polycythemia vera for 2 years. He had a brief terminal illness marked by renal failure. Necropsy revealed multiple myeloma.

**Discussion.** It is of interest to speculate upon the part played by the myeloma in causing or contributing to the polycythemia in each of these cases. No attempt will be made to delve extensively

\* The authors wish to express their thanks and gratitude to Dr. N. Rosenthal and Dr. L. Davidson for permitting us to include this case.

sively into the etiologies and origins of myeloma and polycythemia vera, which appear to be neoplastic in nature. However, it is possible that the proliferating cells of both the red cell and myeloma series originate from the same stem cell with certain factors, unknown at present, determining the type of cell produced. In these cases, the stem cell may first have differentiated into the red cell series to cause the elevated red cell count which later decreased when the stem cell differentiated into myeloma cells. One can only speculate as to the part played by altitude and pulmonary disease in contributing to the polycythemia. The myeloma may also have a relation to polycythemia comparable to that of leukemia where the latter often follows or complicates polycythemia vera<sup>11</sup>.

In Case 1, the lack of a favorable symptomatic response of the patient to radioactive phosphorus is worthy of consideration. Although the red cell count fell to normal levels, the patient's symptoms persisted after temporary improvement. It is possible that the presence of unrecognized myeloma at the onset which may have been temporarily benefited by P<sup>32</sup> may have been chiefly responsible for most of the patient's symptoms, instead of the polycythemia. This suggests the importance of looking for other diseases in polycythemia patients who do not respond well to therapy.

Some question arises as to the relation between the myeloma and the radioactive phosphorus in Case 1. Could the phosphorus be a factor in causing the appearance of the myeloma? There is no record of such an occurrence in the literature. The lack of knowledge of whether this patient had myeloma before or during phosphorus treatment makes it impossible to attempt to answer this question; but with our present knowledge concerning the induction of

tumors after irradiation, it is unlikely that such small doses could possibly induce a neoplasm so soon after radiation therapy. Also, to date there have been no evidences of similar or other delayed effects of P<sup>32</sup> in an experience with several hundred patients extending over the past 13 years. Another question arises: if the patient did have latent myeloma, did it respond therapeutically to the phosphorus therapy? This also cannot be answered but must be considered in view of a recent report by Bayrd and Hall<sup>12</sup> of a complete remission for a known 19 months of myeloma following 6 millicuries of radioactive phosphorus, and in view of some improvement in several patients with myeloma treated with radioactive phosphorus<sup>9</sup>.

The occurrence of myeloma in the other 3 cases which never received radioactive phosphorus or Roentgen ray therapy adds further support to the view that radioactive phosphorus is not an etiological factor in the myeloma of Case 1.

Since these patients were studied initially for their polycythemia, the unexpected discovery of myeloma provides some information about the course of the latter disease. In Case 2, the patient has shown no symptoms which can be definitely attributed to the myeloma for 1 year since its discovery. This indicates that myeloma can be present in a latent state and this situation may well apply to the other cases reported here. At present, very little is known about this latent state and its duration.

**Summary.** A review of the literature has revealed that there are 2 reports of polycythemia associated with possible myeloma. Two cases of polycythemia with Bence-Jones proteinuria have also been described in the literature.

Four cases of polycythemia and definite myeloma are herewith reported.

All cases were first studied and followed because of their polycythemia, and the myeloma was an unexpected development or finding.

Some interesting questions suggested by these cases are discussed: the rela-

tion of myeloma to polycythemia and their etiologies; response of polycythemia to radioactive phosphorus; radioactive phosphorus as a therapeutic agent in myeloma, and the latent period of myeloma.

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# VENOUS THROMBO-EMBOLIC PHENOMENA°

## THEIR ABSENCE IN PARAPLEGIC AND TETRAPLEGIC PATIENTS

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FATAL thrombo-embolic phenomena have been cited as some of the undesirable results of prolonged bed rest<sup>1,2,17,20,27,30</sup>. Such studies<sup>3,12,24,26</sup>, however, have not represented clearly the factor of bed rest in relation to the incidence of pulmonary embolizations, since no correlation has been made between both the length of time of bed rest and that of the incidence of emboli in the lungs. In addition, the term bed rest has been used with too broad a definition, and has not represented the same situation as the term prolonged immobilization would imply. This latter phrase describes more adequately those circumstances which have been reported to favor the development of phlebothromboses and subsequent embolic phenomena in the venous system.

In the past 17 months on the neurosurgical wards of the United States Naval Hospital, St. Albans, New York, there have been 45 patients, 14 of whom have been unable to move voluntarily those muscles innervated by nerve fibers from the low cervical, thoracic, lumbar, and sacral segments of their spinal cords. The remainder of these men represented instances of either anatomic or physiologic spinal cord interruptions below the cervical spinal cord segments. The total time in which

their paralyzed parts had not been moved was 115 man-years. During this time they had been subjected to approximately 175 surgical procedures of various kinds, but primarily those performed by the neurologic, urologic, and plastic surgery services. There have been five deaths, and post-mortem examinations of tissues, other than the spinal cord, were carried out in four instances.

Since these patients represented in many respects the classical situation for the development of fatal pulmonary embolizations, it is the purpose of this study to evaluate the absence of these phenomena in these men.

**Methods of Study.** Those 3 etiologic factors which have been reported to favor the development of venous thromboses and fatal pulmonary emboli were considered<sup>22,30</sup>: 1. Blood factors. 2. Processes which alter the condition of the vein wall and retard the venous return to the heart from the lower extremities. 3. Generalized processes favoring thrombo-embolic phenomena.

As has been noted before, the patients studied had either an anatomic or physiologic interruption of their spinal cords. The average age of the entire group was 26.1 years; the oldest being 43 years and the youngest 20 years. The determinations listed in Table 1 were performed on a group of 15 of these men and were done when the following conditions prevailed: 1. Surgery had not been performed in the previous 7 days. 2. Penicillin, sulfonamides and streptomycin had not

\* The opinions of the authors expressed herein do not necessarily represent those of the Bureau of Medicine and Surgery of the Navy Department or of the Naval Service at large.

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**TABLE 1.--BLOOD FACTORS IN 15 PARAPLEGIC AND  
TETRAPLEGIC PATIENTS**

|     | Patient | Spinal Cord Level | Prothrombin Time (% Normal) | Coagulation Time (Min.) † | Bleeding Time (Min.) ‡ | Blood Platelets (Per c.mm.) § | Blood Total Protein (Gm. per 100 cc.) ** | Serum Albumin (Gm. per 100 cc.) ¶ | Serum Globulin (Gm. per 100 cc.) # | Blood Calcium (mg. per 100 cc.) *** |
|-----|---------|-------------------|-----------------------------|---------------------------|------------------------|-------------------------------|--|-----------------------------------|------------------------------------|-------------------------------------|
| 1.  | R.H.    | T 7               | 90                          | 8                         | 2.5                    | 237,000                       | 6.62                                     | 4.10                              | 2.52                               | 10.91                               |
| 2.  | P.M.    | T 4               | 100                         | 2                         | 3.2                    | 182,000                       | 6.10                                     | 4.10                              | 2.00                               | 10.75                               |
| 3.  | A.W.    | L 1               | 98.1                        | 6                         | 2.9                    | 210,000                       | 7.40                                     | 4.65                              | 2.75                               | 10.54                               |
| 4.  | W.D.    | T 10              | 89                          | 5                         | 2.4                    | 181,000                       | 9.10                                     | 3.95                              | 5.50††                             | 11.40                               |
| 5.  | A.M.    | T 9               | 100                         | 6                         | 2.0                    | 190,000                       | 6.70                                     | 3.65                              | 3.05                               | 10.91                               |
| 6.  | L.L.    | T 10              | 100                         | 8                         | 2.8                    | 188,000                       | 6.55                                     | 3.87                              | 2.68                               | 13.36                               |
| 7.  | P.Y.    | T 5               | 90                          | 2                         | 3.0                    | 193,000                       | 7.90                                     | 3.00                              | 4.90                               | 11.06                               |
| 8.  | W.M.    | T 12              | 100                         | 7                         | 3.1                    | 186,200                       | 7.10                                     | 4.15                              | 2.95                               | 10.69                               |
| 9.  | H.V.    | C 6               | 100                         | 3                         | 2.35                   | 175,000                       | 7.60                                     | 4.70                              | 2.90                               | 11.94                               |
| 10. | F.D.    | C 6               | 100                         | 5                         | 3.0                    | 201,000                       | 6.65                                     | 4.49                              | 2.16                               | 9.88                                |
| 11. | S.K.    | T 5               | 100                         | 4                         | 2.5                    | 195,000                       | 6.50                                     | 4.65                              | 1.80                               | 12.18                               |
| 12. | J.C.    | T 9               | 89                          | 8                         | 1.8                    | 183,000                       | 6.70                                     | 4.65                              | 2.05                               | 10.90                               |
| 13. | E.W.    | T 6               | 95                          | 2                         | 2.0                    | 184,000                       | 6.30                                     | 3.45                              | 2.85                               | 10.82                               |
| 14. | W.H.    | L 1               | 88                          | 7                         | 2.7                    | 200,000                       | 7.10                                     | 3.80                              | 3.30                               | 10.29                               |
| 15. | C.F.    | T 12              | 89.8                        | 2                         | 1.9                    | 180,000                       | 6.50                                     | 3.95                              | 2.60                               | 11.19                               |

\* Link - Shapiro Method; The Maltine Company, New York, New York

† Lee - White Method (20); Normal Values (minutes) - 5-8

‡ Duke Method (29); Normal Values (minutes) - 1-3

§ Fonio's Indirect Method (6); Normal Values (c.mm.) - 180,000-220,000

\*\*¶ Greenberg Method (21); Normal Values (gm. per 100 cc.) -  
Total Protein 7.1 ; Albumin 4.1; Globulin 2.7

\*\*\* Clark-Collip Modification of the Kramer - Tisdall Method (17)  
Normal Values (mg. per 100cc.) 9-11.5

†† Abnormal results such as this will be discussed in a future communication from a different standpoint.

been administered in the past 72 hours. 3. Fever was absent. 4. Vitamin "K" had not been given in the previous week.

It was necessary to observe these precautions because of the effects of Vitamin "K" and drugs such as penicillin on the prothrombin time and coagulation time, respectively. Also, Selye<sup>32</sup> had shown that following certain stimuli an alarm reaction was produced in which there was a decrease in the blood clotting time and an increase in blood platelets. The results of the blood total protein, serum albumin, and serum globulin determinations were included because of Quick's<sup>31</sup> opinion that the serum albumin represented the normal antithrombin of blood, and because of Ochsner's<sup>29</sup> belief that hypoproteinemia and hyperglobulinemia were among the causes of the increased coagulability of blood following tissue trauma.

The second and third factors were studied by clinical observations of these patients on the wards.

**BLOOD FACTORS.** Although it was quite evident to us that there was no one group of determinations which we could have made to estimate exactly a normal or an abnormal clotting mechanism in these patients, we deemed the procedures noted in Table 1 adequate for this study. Our purpose in estimating these individual factors was merely to answer the question whether or not the blood of these men contained these factors in quantities sufficient for normal blood coagulation. We considered this the only accurate information we could gain from these procedures, since, we too, agree with DeTakats<sup>7</sup> concerning the unreliability of these tests in establishing an increased blood clotting tendency.

The results of most of the determinations were within the accepted normal range for the individual test. Even those results which were abnormal con-

firmed the fact that the ability of the blood of these patients to clot was not subnormal. Since this was the case, we felt that the blood clotting mechanism in this series of patients should react to extraneous influences in a fashion similar to that of other bedridden patients. Deitrick's<sup>5</sup> findings on immobilized normal young males were similar to these results.

**VENOUS FLOW AND VEIN FACTORS.** The lower extremities of these patients were almost constantly being subjected to the pressure of a bed or a wheelchair. The muscles of these limbs were atrophied and extreme edema was present in some cases, suggesting the presence of circulatory insufficiency. Although no direct measurement of the venous blood flow in the lower extremities of these patients was made, the observations of Wakim *et al.*<sup>34</sup> on the venous blood flow in the lower extremities of patients with normal, spastic, and flaccid muscles amply demonstrated that in cases of flaccid paralysis there was only an insignificant increase in the venous blood flow when stimulation of the muscles was attempted. Dock<sup>11</sup>, in fact, has also observed the presence of organized thrombi in the veins of flaccid lower extremities of patients who have died of acute anterior poliomyelitis and presumably the basis of this finding was that of venous stasis in the flaccid muscles. These observations and those of Franklin<sup>15</sup> confirm the accepted opinion of the role of muscle contraction in returning venous blood to the heart from the lower extremities and add support to the suggestion that circulatory insufficiency was present in the lower extremities of the patients of this series.

Originally it was thought that the presence of intermittent and, in some cases, almost continuous spasms of the musculature in the lower extremities of some of these men may have prevented

any considerable degree of venous stasis and, thus, have been the important factor in preventing thrombo-embolic episodes. However, in those men in whom the spasmodic contractions of the muscles in their lower extremities were most severe, surgical division of the anterior spinal nerve roots to these muscles was performed, rendering them flaccid. Since there has also been no fatal thrombo-embolic event in these patients after their muscles have been flaccid, it is evident that the presence of spasticity of the muscles in the lower extremities of some of these men has little to do with the absence of thrombo-embolic episodes in these instances.

Local conditions such as those that have been enumerated<sup>4,9,10,16,24,25</sup> and which Ferguson<sup>13</sup> deemed exceedingly important, must, if other expressed views regarding venous thromboses are to be maintained, be considered favorable for the development of phlebotromboses and pulmonary embolizations.

**GENERALIZED FACTORS.** These patients have been subjected to innumerable surgical procedures which, in themselves, have been reported<sup>20</sup> to increase the coagulability of blood and, together with the other processes mentioned, should increase the probability of fatal pulmonary embolizations in these instances. It is significant also that until recently many of these men received large quantities of analgesic and hypnotic drugs which, according to Dock<sup>9</sup>, increase the probability of venous thromboses and pulmonary accidents in bed-rest patients. All those other processes such as repeated infections, tissue destruction, and general debilitation were also present in many cases. In the tetraplegic patients particularly, one other factor, that of the loss of the primary muscles of respiration, was present. This situation along with the almost constantly supine position of

these men created the ideal respiratory basis for the occurrence of lethal thrombo-embolic events in the venous system.

**Discussion.** Even though all the aforementioned processes favoring pulmonary embolizations have been present in these patients, no patient in this series has died as a direct result of this phenomenon. Post-mortem studies of 4 patients, also, did not reveal any evidence of old pulmonary infarctions. However, we feel that there is still one factor, that of the age of these patients, which will reconcile this conflict.

Allen<sup>1</sup> stated that 82.3% of his patients with venous thromboses were above the age of 40, and Veal and Hussey<sup>23</sup> found that 70% of their 80 cases of venous thromboses were above 40 years old. Evans<sup>12</sup> presented a series of 52 cases of fatal pulmonary embolizations in which the greatest incidence occurred in the 6th decade, and Carlotti *et al.*<sup>3</sup> have demonstrated that 83.8% of their cases of pulmonary embolism in medical patients at the Massachusetts General Hospital between the years of 1936-1940, and 87.4% between the years 1941-1945, were over 40 years of age. Linton<sup>22</sup>, in fact, believes age to be of such importance that he advocates the use of Dicumarol only for the prevention of venous thromboses and pulmonary embolizations in those patients in the older age groups. Studies of this kind emphasize the importance of age in these diseases.

In this group of patients there was only 1 individual above the age of 40 (age 43), and the average age of the entire series was 26.1 years. It appears that it is the existence of this young average age which accounts, in part, for the absence of fatal pulmonary embolizations in these men. The report of Fox *et al.*<sup>14</sup> on the low incidence of fatal pulmonary infarctions in patients with tuberculosis at the Sea View Hospital<sup>1</sup>

Staten Island, New York, also tends to support this assumption.

Although we are unable to explain exactly the role of age in thrombo-embolic venous processes, there is some evidence that may help resolve this problem. Holmgren and Wilander<sup>19</sup>, utilizing the fact that heparin is intensely stained with toluidine blue, found that the granules of the mast cells stain precisely like heparin, thus indicating that these granules are the source of heparin in the body. Furthermore, Jorpes<sup>21</sup>, citing further work of Holmgren, states that there is a steady and considerable decrease in the number of mast cells during the course of life. It may be speculated that it is this steady decrease in the human source of heparin, together with other predisposing factors, that accounts for the occurrence of thrombo-embolic phenomena in patients primarily over 40 years old.

**Summary and Conclusions.** The observation is made that a group of 45 paralyzed veterans represent a total of 115 man-years in which their lower extremities have not been moved vol-

untarily. They have been subjected to approximately 175 surgical procedures. Up to the present there has been no death in this group from a pulmonary embolus.

Data concerning the coagulation mechanism of the blood of these patients are presented and shown not to be consistent with the idea that the blood of these patients clots subnormally. Other factors producing injury to the vein walls in the lower extremities and favoring venous stasis in these limbs are reviewed.

From the data obtained we believe that the following conclusions are warranted: 1. The young average age of the patients in this group accounts for the absence of fatal pulmonary embolizations; 2. The age of bed-rest patients is one of the chief determinants of the occurrence of lethal thrombo-embolic phenomena; 3. The basis for the influence of advancing age on the incidence of thrombo-embolisms may be, in part, the concomitant decrease in the human source of heparin, the mast cells.

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# EXPERIENCES WITH 116 JUVENILE CAMPERS IN A NEW SUMMER CAMP FOR DIABETIC BOYS

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THE present report summarizes experiences and clinical findings with 116 diabetic boys cared for in the newly opened Elliott P. Joslin Camp in the town of Charlton, Massachusetts. Although physicians of the George F. Baker Clinic in Boston have for 18 years sponsored the Clara Barton Birthplace Camp for Diabetic Girls in North Oxford, Massachusetts, and sporadically have sponsored summer camps for boys at various other locations, this was the first year that a permanent camp had been established for boys. Like the Clara Barton Birthplace Camp, it is operated by the Association of Universalist Women of America.

The camp is run as a non-profit organization with fees for campers in 1948 ranging from \$0 to \$5 per day depending upon the statement of the parents as to their ability to pay. No additional charge was made for insulin or for medical and nursing care.

The camp site occupies some 65 acres of hilly, wooded land about 50 miles from Boston and 12 miles from Worcester. It includes a small lake of about 15 acres. Beginning in September, 1947, construction of buildings was started and at the time of the opening of camp on June 26, 1948, 7 campers' cabins, a cooks' cabin, a dining hall, administration building,

laboratory and infirmary were available for occupancy. The campers' cabins were arranged on a hillside overlooking the lake; each accommodated 8 boys and 2 counselors. The boys were arranged in cabins according to age. Personnel included a director, business manager, 14 counselors, 2 cooks and 2 assistants, 3 laboratory technicians, one resident physician and 2 graduate nurses.

The infirmary included quarters for the resident physician and family, 2 nurses, a central office and accommodations for 5 patients in 4 rooms. Only patients with minor illnesses were kept in the infirmary; others were transferred to the New England Deaconess Hospital in Boston. The laboratory building is made of brick with concrete flooring so that it is possible to use apparatus such as the photoelectric colorimeter and microscope as in the usual laboratory. Facilities were available for the determination of sugar in the urine and blood as well as for the routine analysis of urine and simple blood studies, such as hemoglobin and blood counts.

CAMP ROUTINE AND PROGRAM. *Non-medical.* The camp routine was made to conform as nearly as could be to that of the average summer camp for boys. From 7:00 a. m. to 9:00 p. m. a

program was arranged that included in the morning, afternoon and evening, periods of active exercise, such as land sports, swimming instruction and boating, and less active periods such as shop work, crafts, nature study, archery, dramatics and music. The time of the active periods was varied, depending upon the type of insulin being used, so as to decrease both glycosuria and insulin reactions as far as possible.

*Medical.* Every effort was made to treat the diabetic condition as well as or better than under hospital conditions. All food was weighed using gram scales. The 24 hour amount quantity of urine was measured daily and the percentage of sugar determined by the Exton modification<sup>2</sup> of the Sumner<sup>7</sup> reagent for the estimation of urine sugar adapted for use with the photoelectric colorimeter. In addition, specimens of urine were tested qualitatively for sugar at 7:15 and 11:15 a. m. and at 4:15 and 8:00 p. m. Capillary blood sugar determinations were made on each boy twice weekly; on half the group this was done on Monday and Thursday and the other half on Tuesday and Friday. The method of Folin<sup>3</sup> adapted for use with the photoelectric colorimeter was used. During the camp stay a complete physical examination and a complete analysis of urine were made and the blood hemoglobin and red blood count determined. Other special studies which were carried out will be described later.

Except on the morning on which blood sugar determinations were made, campers were given, routinely, 100 gm. of orange juice on arising, following which insulin was administered by one of the nurses. On days on which blood sugar determinations were made, these were taken on arising, following which orange juice and insulin were given. Between meal feedings were given in

the forenoon, afternoon and at bedtime. The exact time and amount of these lunches was varied depending upon the type of insulin being used. Thus, when a combination of crystalline and protamine zinc insulin was given, between meal feedings consisted usually of 2 crackers (each 2½ inches square) at 10:00 a. m. and 8:00 p. m. and 1 such cracker at 2:00 and 4:00 p. m. As will later be brought out when NPH-50 insulin was used, it was usually found best to omit the forenoon lunch and to increase the bedtime lunch so that with some campers the latter included 4 crackers, 180 to 240 gm. of milk and 30 gm. of cheese.

*Summary of Data Regarding Campers.* In all, 116 diabetic boys (1 camper did not require insulin) were accommodated at the camp for periods ranging from 1 to 8 weeks. Of the total number, 2 boys remained for 1 week; 27 for 2 weeks; 1 for 3 weeks; 73 for 4 weeks; 1 for 5 weeks; 5 for 6 weeks; and 7 for 8 weeks. Table 1 gives general data regarding the ages of the boys, duration of diabetes, total insulin dose on admission and discharge, and diet on admission and discharge.

It will be noted that there were 5 campers below the age of 5 years. Although they did surprisingly well in camp, the general consensus was that they were scarcely mature enough to receive the maximum benefit from camp.

Most of the campers were from Massachusetts, but 14 states in all were represented and one of the boys listed in the accompanying table as from New York actually was from Argentina.

#### GEOGRAPHICAL LISTINGS

|               |    |               |   |
|---------------|----|---------------|---|
| Massachusetts | 61 | New Hampshire | 3 |
| New York      | 11 | Rhode Island  | 1 |
| Connecticut   | 9  | Virginia      | 1 |
| Vermont       | 7  | Maryland      | 1 |
| Maine         | 5  | Oregon        | 1 |
| New Jersey    | 5  | Pennsylvania  | 1 |
| Ohio          | 3  | Florida       | 1 |

## ANALYSIS OF HOME TREATMENT

\* PRIOR TO CAMP STAY. Since many of boys arrived at camp showing much sugar in the urine and even diacetic acid, it was thought worth while to attempt to gain some idea as to the adequacy of treatment under home conditions. In 41 of the 116 boys, the first overnight quantity of urine contained more than 2% sugar and in 16 instances gave a positive test for diacetic acid. An even greater number, 23, showed diacetic acid in the first complete 24 hour amount collection.

A detailed, yet simple, questionnaire was filled out under the physician's supervision regarding usual care of the diabetic condition at home. In all, 83 boy completed questionnaires. The information obtained may be summarized as follows.

*Diet.* Of the 83 campers, 32 stated that they weighed their food, whereas 22 said that household measures were used. Twenty-four merely approximated the amount of food taken but only 3 admitted that they ate freely. These statements from the boys themselves as to care in diet would be heartening if it were not for the fact that 51 stated that in addition to their regular diet they frequently took additional food which in the case of some of the campers amounted to a remarkable increase in diet. In answer to the question "Do you follow your diet?" 35 responded in the negative and an additional 16 stated that they frequently broke their diet. Thus, from the testimony of the campers themselves, a total of 51 (61%) did not follow their diet regularly at home.

*Insulin.* Sixty-six campers stated that they knew how to give insulin but only 27 of the 83 said that they usually gave it to themselves alone or under supervision. Seventeen of the 83 gave it to themselves part of the time. Forty of the 83 did not give any supplementary insulin if tests were bad.

TABLE 1.—SUMMARY OF DATA REGARDING 116 CAMPERS

| Age Group (yrs.) | Number | Duration Diabetes Mellitus (yrs.) | Insulin Units |     |       | Admission |     |           | Diet |      |     | Discharge |     |      | Cal. |
|------------------|--------|-----------------------------------|---------------|-----|-------|-----------|-----|-----------|------|------|-----|-----------|-----|------|------|
|                  |        |                                   | CI            | PZI | Total | Discharge | C   | P (grams) | F    | Cal. | C   | P (grams) | F   | Cal. |      |
| 3-4.9            | 5      | 1.8                               | 8             | 13  | 21    | 20        | 155 | 69        | 78   | 1598 | 165 | 78        | 81  | 1701 |      |
| 5-7.9            | 16     | 3.2                               | 6             | 14  | 20    | 26        | 165 | 78        | 84   | 1728 | 195 | 90        | 92  | 1948 |      |
| 8-9.9            | 17     | 3.1                               | 10            | 20  | 30    | 27        | 185 | 87        | 81   | 1817 | 197 | 91        | 103 | 2079 |      |
| 10-11.9          | 30     | 4.5                               | 7             | 22  | 29    | 29        | 203 | 97        | 95   | 2055 | 213 | 112       | 111 | 2299 |      |
| 12-13.9          | 27     | 5.3                               | 15            | 29  | 44    | 36        | 207 | 108       | 107  | 2223 | 220 | 124       | 120 | 2456 |      |
| 14-16.3          | 21     | 5.5                               | 17            | 38  | 55    | 43        | 222 | 113       | 111  | 2339 | 236 | 134       | 126 | 2614 |      |

*Urine Tests.* Of the 83 boys, 52 stated that they tested their urine under home conditions and all but 18 stated that they made tests at least once daily. In 24 instances it was stated that tests were done daily 4 times. Twenty-one boys stated that the urine tests at home with Benedict's solution usually ranged from a yellow-green to a red reaction. It is our impression from observations during the early days at camp that the number showing bad results was probably greater than this.

*Insulin Reactions.* With only a few exceptions the campers had been at home on a combination of crystalline and protamine zinc insulin taking the two varieties by separate injection the morning before breakfast. Sixty-eight stated that they were subject to insulin reactions, thus indicating the importance of this complication in the every day life of the juvenile diabetic. Forty of these stated the most common time of reaction was between 4:30 p. m. and bedtime and the least common time was between 11:30 a. m. and 4:30 p. m. Only 53 of the 83 campers stated that they usually carried with them some form of carbohydrate, usually candy or sugar wafers.

*Periodic Examinations.* In 37 of the 83 boys it was stated that they visited

their doctor once or twice a month; 23 every 2 to 3 months; and 19 every 4 to 12 months. Most patients stated that a blood sugar determination was taken at the time of each visit to the doctor.

*CLINICAL EXPERIENCE DURING CAMP-ING SEASON.* Under the intimate conditions in a summer camp the resident physician had an unparalleled opportunity for clinical observations among the sizable group of diabetic boys. At the outset it was decided that the aim of treatment would be to secure as far as possible freedom from sugar in the urine and a normal blood sugar. It was realized from the beginning that a compromise would need to be made with this ideal to provide relative freedom from insulin reactions. It was early found, however, that from a practical standpoint such freedom was impossible if one were to strive for meticulous control. However, a detailed perusal of the day by day charts shows that in most instances following the first few days in camp glycosuria was kept on the average below 10 gm. per 24 hours and in many instances below 5 gm. per 24 hours. Thus, as it actually worked out, in very few campers was there a wastage of more than 5% of carbohydrate consumed, and, considering the total glucose content of the

TABLE 2 -COMPARISON OF WEIGHT AND HEIGHT OF NORMAL AND DIABETIC BOYS IN CAMP

| Age, Years | Groups | Number | Weight, Pounds |          | Height, Inches |          |
|------------|--------|--------|----------------|----------|----------------|----------|
|            |        |        | Normal         | Diabetic | Normal         | Diabetic |
| 3          | - 39   | 3      | 28.7-35.3      | 35       | 36.0-38.6      | 40.1     |
| 4          | - 49   | 2      | 31.6-39.2      | 44       | 38.8-41.6      | 42.7     |
| 5          | - 59   | 3      | 35.1-43.5      | 50       | 41.2-44.2      | 46.1     |
| 6          | - 69   | 7      | 39.2-48.6      | 53       | 43.5-46.5      | 47.0     |
| 7          | - 79   | 6      | 43.0-53.2      | 55       | 45.6-48.8      | 50.5     |
| 8          | - 89   | 9      | 47.2-58.4      | 63       | 47.5-50.9      | 51.7     |
| 9          | - 99   | 5      | 51.6-64.4      | 68       | 49.5-52.9      | 54.4     |
| 10         | - 109  | 8      | 57.0-71.6      | 72       | 51.4-55.0      | 55.1     |
| 11         | - 119  | 12     | 63.0-79.4      | 81       | 53.3-57.1      | 57.6     |
| 12         | - 129  | 15     | 69.4-87.2      | 86       | 55.2-59.0      | 58.4     |
| 13         | - 139  | 9      | 75.9-95.7      | 95       | 56.9-60.9      | 58.5     |
| 14         | - 149  | 18     | 81.1-102.9     | 121      | 58.6-62.8      | 61.1     |
| 15         | - 159  | 12     | 89.4-113.4     | 105      | 60.3-64.5      | 65.7     |
| 16         | - 169  | 2      | 98.0-122.0     | 127      | 61.8-66.2      | 66.6     |

diet arising from carbohydrate, protein and fat sources, the wastage of sugar was on the average less than 3 to 4%.

The health and vigor of the campers was in general at a high level, at least equalling that of non-diabetic boys of comparable age. As a gross index of this, one may cite the fact that in baseball games with neighboring camps (non-diabetic), 4 of the 5 games were won by the diabetic boys; the only swimming meet and both of two track meets were won by the diabetic boys.

From the summary of heights and weights of boys in Table 2 it is obvious that they compare favorably with figures of normal standards.<sup>1</sup> In fact, almost without exception the diabetic boys were taller and heavier than expected from normal standards. Although weight gain during the camp season was negligible, it must be pointed out that the boys lived during their period of 2 to 4 weeks under conditions of fairly strenuous activity.

*Diet.* As shown in Table 1, the average diet at discharge ranged from 165 gm. of carbohydrate daily for patients from 3 to 4.9 years of age to 236 gm. in patients from 14 to 16.3 years. Corresponding figures for protein and fat were 78 to 134 gm., and 81 to 126 gm., respectively. The caloric content of the diet ranged from 1701 for the younger group to 2614 for the older group. The lowest diet in the camp was carbohydrate 150, protein 77, and fat 77 gm., and the highest diet was carbohydrate 253, protein 154, and fat 143 gm. These discharge diets varied somewhat from the diets during the camp stay, although not greatly so. It was early found certain increases would be imperative from previously set levels in order to satisfy requirements of appetite and energy expenditure. The carbohydrate content of the diet was distributed about equally among the 3 main meals. Between meal feedings were given as previously described.

*Insulin.* With few exceptions, boys on entrance to camp were first treated with crystalline and protamine zinc insulin by separate injection in the morning before breakfast. Only rarely was supplementary crystalline insulin given before the noon and evening meal. Following initial adjustment and accumulation of basic data, the campers were then shifted to a new modified protamine insulin (Eli Lilly and Company, NPH-50),<sup>5</sup> or to a combination of crystalline and globin insulin with zinc given by separate injection before breakfast. With 34 campers enough time was available to permit return to the program of crystalline and protamine zinc insulin and then another study period on the insulin under investigation.

The results of the special insulin studies have been made the subject of a separate communication<sup>4</sup> and will not be given in detail here. However, it is appropriate to state that the NPH-50 insulin gave promising results and with almost all campers it was possible to achieve as good or better control with a single dose of this type of insulin as with the combination of crystalline and protamine zinc insulin. In a number of instances it was possible to use an appreciably smaller dose of NPH-50 than the total dose of the other 2 varieties. With the relatively few campers with whom globin insulin with zinc (Lilly) was given, the results were not unfavorable. However, in no instance could it be said that the results obtained were better than with other programs. With the most severe diabetics, the length of action of globin insulin with zinc did not seem long enough to provide a satisfactory fasting blood sugar.

*Exercise.* If, prior to the camp experience, there had been any doubt in the minds of medical attendants as to the remarkable effect of physical exercise upon the blood sugar of pa-

tients receiving insulin, that doubt would have been quickly dispelled. All concerned acquired great respect for the powerful hypoglycemic effect of exercise under the conditions prevailing in camp. Using an active program it was possible to give much higher diets and maintain as good or better control of diabetes with a lower dose of insulin. Days of relative inactivity promptly produced increased hyperglycemia and glycosuria. The physician was able to reduce glycosuria at certain times in the day when it otherwise would have occurred by suggesting an active physical program at such hours. The time and size of between meal lunches had to be arranged to correspond with the point of maximum activity of the insulin currently used.

*Insulin Reactions.* It must be confessed that insulin reactions occurred with relative frequency. In all, 648 reactions occurred during 3050 camper days. There was an average of about 11 reactions on each of the 56 days at camp. On 1513 camper days during which a combination of crystalline and protamine zinc insulin was used, there were 273 reactions (18%); on 120 camper days when a combination of crystalline and globin insulin (Lilly) was used there 41 reactions (34.1%); and on 1396 camper days during which time NPH-50 insulin was used, there were 320 reactions (22.9%). It is evident that under the conditions of study, reactions were most common when a combination of crystalline and globin insulin was used. Most reactions were mild and responded readily to treatment with 2 to 4 gm. of sugar given in the form of dextrose wafers. Others required 100 cc. of orange juice or ginger ale for treatment, but in only 36 instances was it necessary to give glucose intravenously. It was a rule of camp to treat reactions promptly and adequately so that the camper was able

to resume his activity without delay. Thus patients took part in the normal camp program, including competitive sports, despite the fact that they may have been treated for hypoglycemia earlier in the day even to the extent of having received glucose intravenously. In no instance was any late complication of hypoglycemia observed.

*MEDICAL COMPLICATIONS.* The general health of the campers was amazingly good. There were 10 admissions to the infirmary during the entire camp season and in only 4 instances was it necessary to retain the camper in the infirmary for longer than 2 days. No instance of communicable disease was encountered, except 4 cases of "pink eye"; no instance of fracture of bones occurred; no acute surgical emergency arose. Illnesses were confined to upper respiratory infections, cuts and abrasions, epidermophytosis, poison ivy dermatitis and similar minor ailments.

The infirmary was kept open all hours of the day and night and regular sick call was held at 9:15 a. m. and 1:15 p. m. Excluding routine and special physical examinations, there were 525 infirmary calls recorded during the 8 week period.

Only two campers were transferred to the New England Deaconess Hospital, one because of infection of a foot and sprained ankle, and the other for study of a chronic obscure neurological condition. One other patient was discharged to his home because of an upper respiratory infection from which he quickly recovered and was able to return to camp.

*Eyes.* Careful ophthalmoscopic examination was carried out in 109 boys by Dr. Henry A. Mosher of Boston to whom we are indebted for the following summary: "Of those with notable findings, 3 boys had hemorrhages and exudates in their fundi. Of these, a boy, aged 8.3 years, who had been diabetic for 6 years had a group of five small

round, deep hemorrhages in one eye only. Another, aged 9.9 years, a known diabetic for one year, had 10 small, waxy exudates near the macula of one eye only; there were no hemorrhages in either eye. The third boy, aged 15.5 years, a diabetic for 8½ years, had 6 or more deep, round hemorrhages in each macular region and several hemorrhages in the nerve-fibre layers and exudates in both eyes. No definite evidence of arteriosclerosis was seen in the fundi of any of the boys in this group. Two boys had bilateral nuclear lens opacities probably of congenital origin."

The visual acuity of the campers was estimated by the use of Snellen test charts in 84 of the boys. Vision proved to be as good as 20/30 or better in both eyes in all, with the exception of 11 boys in whom the vision in one or both eyes was 20/40 or 20/50 and in 3 instances less than 20/50.

*Teeth.* The teeth of certain of the campers were examined under the supervision of Dr. Harold A. Kent of Boston to whom we are indebted for the following summary: "In a study of 52 boys between the ages of 7 and 16 (a high caries susceptibility period) 7 (about 13%) had no fillings or cavities, nor had they lost any teeth due to dental decay. These ages were grouped in order to study the permanent teeth and their caries susceptibility; in the entire 52, no permanent teeth were lost because of extensive caries. Diabetes had been discovered between 1 and 9 years of age or before many of the permanent teeth had erupted. In another group of 13 patients between the ages of 3 and 7, the deciduous teeth in 12 patients were free from dental caries. These findings help to substantiate the statement that if the onset of diabetes occurs before 9 years of age there is a very good chance that these patients can retain their teeth and have healthy mouths during the

high caries susceptibility ages of 3 to 16. As far as could be determined all patients studied had the average professional attention; that is, some were seen regularly by their dentist, others were not."

*Roentgenological Studies.* Because of the well recognized high incidence of arteriosclerosis in diabetics of long standing, it was thought worth while to check roentgenologically those campers whose diabetes was of long duration. In the first half of camp those whose diabetes was of 7 or more years' duration were studied with Roentgen rays of the chest, pelvis and legs, with special technique to bring out slight evidences of arteriosclerosis. Nine such patients were studied with entirely negative results. Consequently, in the latter half of camp only those patients with diabetes of 10 or more years' duration were studied in this way. Four campers with duration of diabetes averaging 10.1 years had Roentgen ray examination. In none of these was there any evidence of arteriosclerosis.

These findings bear out the general experience that in the present day with only moderately good control of diabetes, arteriosclerosis does not begin to appear in demonstrable form until more than 10 years have elapsed and usually not until 15 or 20 years have gone by.

*Capillary Fragility.* Tests of capillary fragility were carried out in 112 campers. Two techniques were employed. In one the blood pressure cuff applied to the upper arm was kept at the level of diastolic blood pressure of the camper for a period of 4 minutes. At the end of that time, the number of petechiae was counted in a circle 6 cm. in diameter below the antecubital space. Employing this procedure essentially negative findings (12 petechiae or less) were secured, with one exception. In one camper 35 petechiae were noted. Two other campers had 8 petechiae,



which is within the normal range, and all others had 4 or less. Most of the boys showed no petechiae.

A second technique was carried out in all by inflating the cuff uniformly to 80 mm. Hg. and maintaining this pressure for 4 minutes. The camper showing 35 petechiae by the first technique likewise showed 35 petechiae by the second method. One of those showing 8 by the first method showed 26 by the second and the other showed 8. By the second method there was a small group with petechiae above 12 in number; these comprised one with 20; one with 16; one with 15; 3 with 14; and two with 13.

With diabetic patients in general it has been found that in those with retinitis there is almost invariably an abnormal capillary fragility.<sup>6</sup> This did not prove to be the case in the group in question. Although it is true that the one patient showing 35 petechiae had retinal hemorrhages and the one showing 8 petechiae showed 4 or 5 small hemorrhages in one eye, no other patient showed retinal hemorrhages. Consequently, the incidence of retinal hemorrhages in this group of patients was small indeed.

*Patch Tests.* Vollmer patch tests for tuberculosis (old tuberculin) were carried out in all patients. Patches were allowed to remain 48 hours and readings made at the time of removal and again in 48 hours after removal. All tests were negative.

*Special Blood Studies.* Determinations of total serum protein were made in 59 campers. In none of these was the value below 5.9 gm. per 100 cc. In 57 cases the value lay between 6 and 8 gm., with an average of 7.1 gm. Serum albumin in 59 campers showed values ranging between 3.6 to 5.6, with an average of 4.58 gm. per 100 cc. Values for serum globulin were above 3.2 gm. in 2 cases and ranged from 1.3 to 3.2 gm. in 56 campers. The aver-

age for the entire group was 2.51 gm. The albumin : globulin ratio was below 1.5 in 14 cases, between 1.5 and 2.5 in 72, and above 2.5 in 3 cases with an average of 1.84 gm. for the entire group.

The average value for plasma cholesterol was 195 mg. per 100 cc. for 57 campers. Included in this group were 4 with values under 140 mg.; 41 with values between 140 and 200 mg.; 37 between 200 and 250 mg.; and 5, 250 mg. or more. Of 5 campers with values of 250 mg. or over, 2 had values of 250 mg., one 270 mg., one 276 mg., and one 312 mg. It was of interest that only one of the 5 appeared to be under poor control on entrance to camp and that only one had been on a diet providing, as prescribed, more than 100 gm. of fat a day.

*Lipodystrophy due to Insulin.* All campers were examined carefully for evidences of lipodystrophy due to insulin. A total of 49 were found to have insulin atrophies; these represented 42.6% of 115 campers who were receiving insulin. Twenty-five had atrophies in the upper extremities and 39 in the thighs and buttocks. Included in this group were 15 who had atrophies in both the arms and the legs. The incidence of insulin atrophy was higher in the younger patients and amounted to 43% of the patients under 11.9 years.

The finding of hypertrophy of fat at the site of insulin injections was found in 42 or 36.5% of the campers. Of these, areas of hypertrophy occurred in 32 campers in the arms and 23 in the legs, and included in the total group were 13 with such areas in both arms and legs.

Certain other campers showed to a greater or lesser degree the third condition which is frequently seen when insulin is given day after day in the same area, namely that of hardened skin and subcutaneous tissue apparently due to infiltration with scar tissue.

*Distinctive Features.* Attempts were made from records of past history and examinations and from careful camp studies to tabulate distinctive features among the group. Of the 116 campers, 23 gave a history of one or more attacks of diabetic coma in the past, 6 had a history of epilepsy, and in 5 of these so studied, electroencephalographic tracings were characteristic of this disease; 5 were under medication for such with phenobarbital and dilantin. From past records there was evidence that 43 had had a palpable liver at some time or other in the past and in the examinations at camp a total of 16 were found to have a liver that descended on inspiration to from being barely palpable to 2 finger breadths below the costal margin. In only one camper could the spleen be felt. This camper, a boy of 8.8 years with diabetes of 6.1 years' duration, also had a palpable liver and 4 or 5 retinal hemorrhages in one eye.

*Discussion.* Observation of this group of diabetic boys left no doubt as to the great benefit of summer camp experience to the children. Furthermore, the period at camp is one of benefit for the parents. The stay provides as good or even better opportunity for reevaluation and regulation of the diabetic condition as study in a hospital. In addition, the diabetic camp affords opportunity for the trial of new methods of treatment under controlled conditions. Camp life allows for control of the influencing factors of diet, insulin and exercise to a degree rarely possible in home or even hospital environment.

Much has been said and written recently regarding the complications, chiefly vascular in nature, which may beset the diabetic and particularly those whose disease has been poorly controlled. One may wonder, therefore, why in this group of patients, complications were relatively infrequent. It must be pointed out that in no case was the duration of diabetes

greater than 12.4 years and then even in the 12 to 16 year old group, the average duration of the disease was only 5.5 years or less. Hence these patients have as yet not had their disease long enough to develop degenerative complications to a degree recognizable clinically. This is the challenge, then, presented to all physicians and other workers in the field: to devise methods of treatment which over 15, 20 or more years of time will protect diabetics from the late complications. The camp experience reported in this paper demonstrates clearly that if conditions approaching the ideal are provided, diabetes even in the juvenile patient can be well controlled. It is not unreasonable to postulate or to hope that if such good control could be consistently maintained, degenerative processes might be avoided or at least greatly delayed.

*Summary and Conclusions.* 1. Clinical experiences in a new summer camp for diabetic boys together with a summary of findings in 116 campers are reported.

2. Ages ranged from 3.3 to 16.3 years and duration of diabetes from 0.3 to 12.4 years.

3. Analysis of home treatment prior to camp stay indicated that in most instances care in diabetes control left much to be desired and tests in more than one-third of the boys on admission indicated laxity in home treatment.

4. The general health and vigor of the diabetic boys compared favorably with that of non-diabetic boys of comparable ages.

5. Almost without exception the heights and weights of diabetic boys were greater than figures given in standard tables for non-diabetic boys of comparable ages.

6. With care as to regulation of diet and physical activity it was found that with a single daily injection of a new modified protamine insulin (NPH-50-

Lilly), as good or better control of hyperglycemia and glycosuria was possible in most campers than with a combination of unmodified and protamine zinc insulin given by separate injection.

7. Results with globin insulin with zinc given in combination with unmodified insulin by separate injection were not unfavorable, except that in patients with severe diabetes the length of action of globin insulin with zinc did not extend sufficiently through the 24 hour period to prevent elevation of the fasting blood sugar.

8. The camp experience gave increased emphasis to the blood-sugar-lowering effect of physical activity when combined with an adequate amount of insulin.

9. Although careful attempts were made to prevent hypoglycemic reactions, their complete avoidance was found impossible when meticulous control of the diabetic condition was sought. However, very few severe reactions were encountered.

10. Funduscopic examination revealed only 3 boys with hemorrhages and exudates. The duration of diabetes in these 3 campers was 8.6, 6 and 1 year, respectively. The boy with duration of 1 year was 9.9 years of age. In this case, only exudates and no hemorrhages were present; the exudates may well not be of diabetic origin.

11. Careful examination of the teeth showed no significant increase in caries over that which might be expected among boys in the general population.

12. In a study of 9 campers with diabetes of 7 or more years' duration, and of an additional 4 with diabetes of 10 or more years' duration, no evidence of arteriosclerosis was found by roentgenographic examinations of the chest, pelvis and legs.

13. Tests of capillary fragility gave findings within normal limits in all but 7 of 112 campers. However, in only 3 campers was the index of capillary fragility appreciably elevated.

14. Vollmer patch tests for tuberculosis were negative in all instances.

15. In none of 89 campers was the value for total serum protein below 5.9 gm. per 100 cc. and in 87 cases the values lay between 6 and 8 gm. The average value for blood cholesterol was 195 mg. per 100 cc. for 87 campers and only in 5 instances was a value of 250 mg. or greater found.

16. Of the 115 campers receiving insulin, 49 showed evidences of atrophy of subcutaneous fat and some 42 showed areas of hypertrophy of fat. Atrophy was most frequent in the lower age groups.

17. Twenty-three of the 116 campers gave a history of 1 or more attacks of diabetic coma in the past. Six had a history of epilepsy and in 5 of these so studied, electroencephalographic tracings were consistent with this disease. Although in 43 campers past records indicated a palpable liver at one time or other in the past, no instances of significant hepatomegaly were found at this time, although in 16 instances the liver could be felt; in only one camper could the spleen be felt.

18. The experience demonstrated again the great value of summer camps both for campers and for their parents. The summer camp is a valuable adjunct in the treatment of diabetic children. It provides opportunity for re-evaluation and regulation of the diabetic condition, for the investigation of new and promising therapeutic measures and for education of diabetic children.

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# INSULIN FAT ATROPHY

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THE irregular disappearance of the subcutaneous fat in some diabetics who receive insulin is a disturbing and as yet unexplained phenomenon associated with the therapeutic use of the hormone. This type of disfigurement has been noted in 20 to 30% of the patients treated with insulin. It occurs more frequently in women and children than in men and, in many instances, is a cause of much concern, if not actual mental anguish, on the part of the patients or their relatives.

**CLINICAL DATA.** In 1926, four years after the introduction of insulin for the treatment of diabetes mellitus, Depisch<sup>7</sup> and Barborka<sup>3</sup> reported the first cases of insulin fat atrophy. Subsequently, clinical surveys of the condition have been made by Fischer<sup>2</sup>, Depisch<sup>4</sup>, Rosenberg and Berliner<sup>17</sup> and Alpert and Ferguson<sup>1</sup>.

Marble and Smith<sup>11</sup> observed fat atrophy in 18.9% of 500 unselected diabetics who had received insulin for 6 months or longer. They found no instance of the abnormality in males over 20 years of age, but Alpert and Ferguson<sup>1</sup> recorded 7 men in this age category in a series of 32 insulin-treated diabetics who exhibited fat atrophy. The data of Marble and Smith<sup>11</sup> revealed also that the female patients with fat atrophy outnumbered the males approximately 7 to 1.

Usually the anatomical regions involved in the atrophic process corre-

spond with those into which the insulin has been injected but rare examples have been reported in which the atrophy occurred at sites remote from those of the actual injection of the insulin<sup>5,10,11</sup>. Except for one instance mentioned by Blotner<sup>4</sup>, all the recorded cases of insulin fat atrophy have been in diabetic patients.

Our experience with insulin fat atrophy, as encountered clinically, has coincided in most respects with that of other writers. The general incidence, however, has been somewhat higher than that shown in the majority of the reported series, in that 31% of our diabetic patients who had received insulin for 6 months or longer showed more or less evidence of the abnormality. No correlation was apparent between the incidence and the degree of fat atrophy and the body weight, the general state of nutrition, the length of existence of the diabetes, the duration of the insulin therapy or the dosage.

**ETIOLOGICAL CONSIDERATIONS.** Various theories have been propounded to explain insulin fat atrophy. Marble and Smith<sup>11</sup> found a significantly higher incidence of so-called allergic disorders in the patients with atrophy than in those without this complication but there is no proof that the atrophy is of the nature of an allergic phenomenon. The acid reaction of crystalline insulin (pH 3.0) has been suggested as a possible cause of the disorder. Since the

condition is associated with the use of protamine zinc insulin (pH 7.3) this implication is scarcely tenable. Carmichael and Graham<sup>6</sup> expressed the opinion that a lipolytic enzyme in the preparations of insulin might be of etiological importance. Rabinowitch<sup>15</sup>, however, was unable to demonstrate the presence of a lipolytic enzyme in commercial insulin. Priesel and Wagner<sup>14</sup> suggested that tricresol, used as a preservative in the insulin preparations, might be the responsible factor. Depisch<sup>8</sup> discounted this possibility since he was unable to induce fat atrophy by the injection of *aqua cresylata* in a patient readily affected by insulin.

There has been some dispute as to whether or not the trauma occasioned

rats made diabetic by partial pancreatectomy. Apparently, the mechanical effect of the injections was not controlled in their experiments by the administration of an innocuous solution into fat pads which did not receive insulin.

EXPERIMENTAL. 1. *Animal Experiments.* In order to confirm the findings of Marble and Smith<sup>11</sup>, an attempt was made to induce fat atrophy in a small group of female rats. Four animals, rendered diabetic by means of alloxan (200 mg. per kg. of body weight subcutaneously), and 3 normal animals were given daily injections of insulin into the fat pad in the right groin of each animal and of an equal volume of physiological saline solution into the

TABLE 1.—ANALYSIS OF FAT PADS FROM DIABETIC AND CONTROL RATS

|              | Rat No. | Wt. of fresh fat pad (gm.) | Side injected with insulin |                                     | Side injected with saline solution |                          | Wt. of ether-soluble material (gm.) |
|--------------|---------|----------------------------|----------------------------|-------------------------------------|------------------------------------|--------------------------|-------------------------------------|
|              |         |                            | Dry wt. of fat pad (gm.)   | Wt. of ether-soluble material (gm.) | Wt. of fresh fat pad (gm.)         | Dry wt. of fat pad (gm.) |                                     |
| Diabetic     | 1       | 0.830                      | 0.624                      | 0.542                               | 0.774                              | 0.594                    | 0.528                               |
|              | 2       | 1.131                      | 0.678                      | 0.520                               | 0.792                              | 0.597                    | 0.510                               |
|              | 3       | 0.565                      | 0.349                      | 0.279                               | 0.494                              | 0.254                    | 0.197                               |
|              | 4       | 0.412                      | 0.216                      | 0.149                               | 0.336                              | 0.173                    | 0.123                               |
| Non-Diabetic | 5       | 1.397                      | 1.091                      | 1.000                               | 1.453                              | 1.116                    | 0.999                               |
|              | 6       | 1.346                      | 1.015                      | 0.921                               | 1.511                              | 1.099                    | 0.933                               |
|              | 7       | 1.637                      | 1.262                      | 1.077                               | 1.630                              | 1.270                    | 1.097                               |

by the repeated injections of insulin may be the cause of the abnormality. This is improbable since the fat atrophy which occurs in narcotic addicts is primarily inflammatory in nature according to Mentzer and DuBray<sup>12</sup>; whereas the histological picture in insulin lipodystrophy includes little, if any, evidence of inflammatory reaction (Mentzer and DuBray<sup>12</sup>; Price<sup>13</sup>).

In an experimental approach to the elucidation of the problem, Marble and Smith<sup>11</sup> described the production of fat atrophy by the injection of insulin into the fat pads in the lower portions of the abdomens and the axillae of 4 male

corresponding fat pad on the opposite side. After a period of 3 months, the fat pads were dissected out and weighed. A small portion of the adipose tissue, of known weight, was removed for histological examination. The remainder was dried to a constant weight, extracted with dry diethyl ether and, after evaporation of this solvent, the ether-soluble material was weighed.

In contrast with the data presented by Marble and Smith<sup>11</sup>, no fat atrophy was obvious by this method of assay at the sites of the insulin injections. Indeed, in 2 of the rats there was actually

slightly more fat demonstrated on the side which received the insulin than on the control side which received the saline solution (Table 1). The comparison to be noted is between the data pertaining to the fat pads on the two sides of each animal. The smaller amount of fat in the diabetic rats, as compared with that in the normal controls, was related, no doubt, to the general weight loss associated with the diabetic state.

The experimental conditions described here differed from those in Marble and Smith's<sup>11</sup> experiments in that the diabetes was produced by alloxan rather than by pancreatectomy;

female rats were used instead of males and the possible effect of trauma was controlled by the injection of isotonic saline solution into the corresponding fat pads on the opposite side of the animals.

In view of the unexpected and conflicting results, additional experiments were undertaken to determine whether the sex of the animals or other observable factors had any bearing upon the apparent discrepancy.

For this purpose, adult white rats of the Wistar strain, each weighing between 200 and 250 g., were selected as follows: *Group A* consisted of 9 male animals; *Group B*, 10 males and *Group*

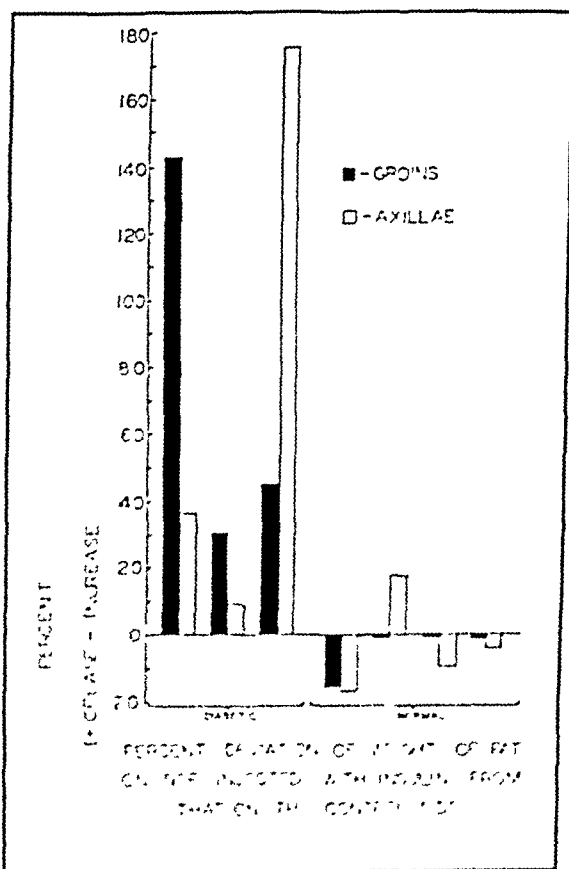


FIG. 1.—Variation in the extractable material derived from the fat pads of the rats in *Group A* (males) which received injections of insulin into the pads on one side of the body. Control injections of saline solution were not given.

C, 9 females. Four rats in each group were designated as controls and each of the others was given a single diabetogenic dose of alloxan. Each diabetic animal received 0.1 ml. of crystalline zinc insulin (10 units per cc.) daily, by injection into the fat pads of the groin and axilla of one side of the body. Each rat in *Groups B* and *C* received also an equal volume of saline solution into the pads of the opposite side. The animals of *Group A* were not given the control injections of saline solution.

At the end of 3 months, the surviving animals were sacrificed and the fat pads were dealt with as described

above. Fig. 1 gives a graphic representation of the results obtained from *Group A*. Obviously, no fat atrophy was apparent. Actually, the amounts of fat at the sites of the insulin injections were increased as compared with the untreated sides in all the diabetic animals. The results from *Group B*, in which the effect of trauma was controlled by the injection of physiological saline solution on the opposite sides, are shown in Fig. 2. Since the relative increase in fat at the sites of the insulin injections was less consistent than in *Group A*, it may be assumed that trauma alone in these particular diabetic rats caused an apparent increase

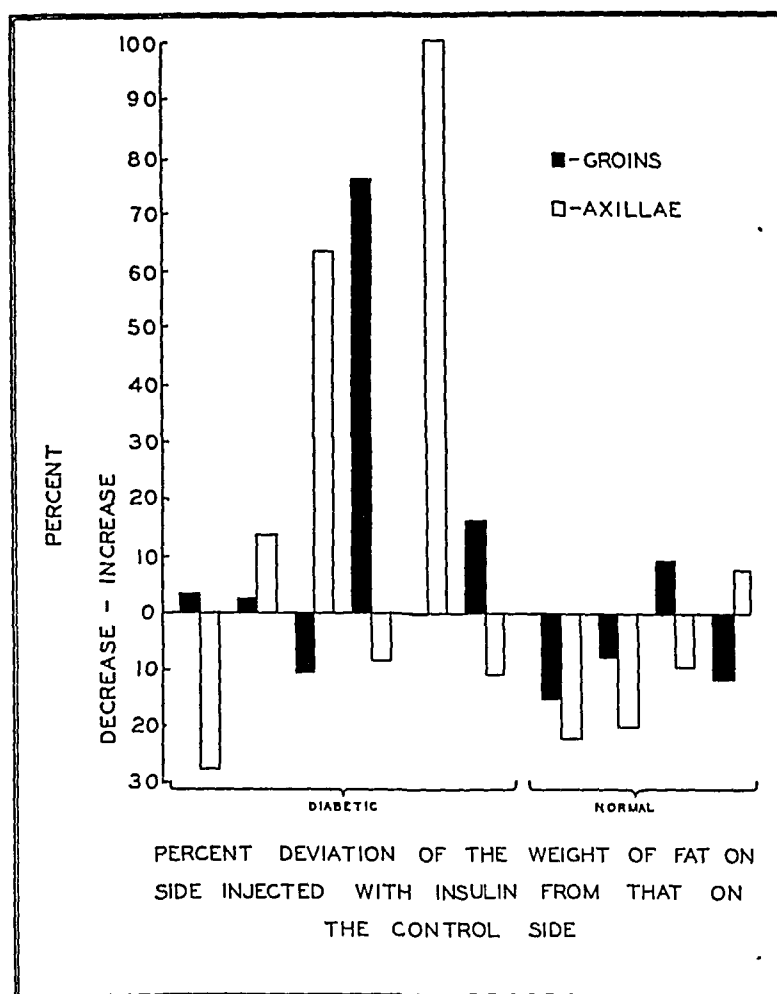


FIG. 2.—Variations in the ether-soluble material derived from the fat pads of the rats in *Group B* (males) which received injections of insulin into the pads on one side of the body. Control injections of saline solution were administered similarly on the opposite side.

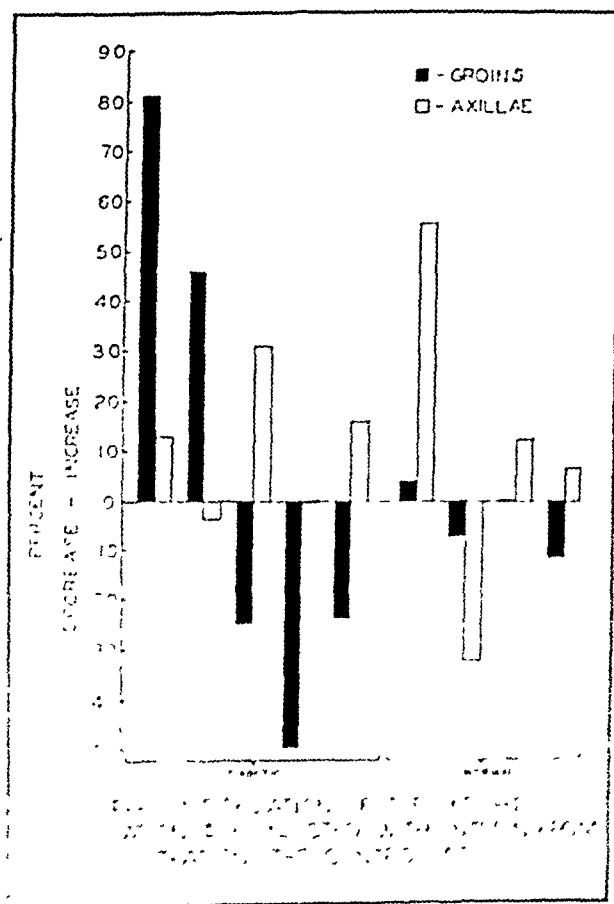


in the local deposit of fat. Such effect of trauma was not evident in the normal rats.

Fig. 3 shows the data from *Group C* in which female rats were treated in exactly the same manner as the males in *Group B*. The results were similar to those obtained with the male animals; hence the indication is that sex, at least in diabetic rats, does not play a rôle in the behavior of fat at the sites of insulin injections. In none of these experiments was there any suggestion of fat atrophy or hypertrophy caused by the injection of the insulin.

2. *Lipase Studies.* Another phase of the investigation relating to insulin fat atrophy was concerned with various factors which might affect the activity of lipase derived from adipose tissue. This seemed to be a logical approach to the problem since lipase doubtless is concerned with the rapid lipid turnover which Rittenberg and Schoenheimer<sup>17</sup> have shown to occur in the fat depots. Any slight alteration in the lipase activity may, therefore, be involved in the production of either fat atrophy or hypertrophy.

An active lipase extract was prepared



from the adipose tissue of surgically amputated human legs, essentially by the method described by Sobotka and Glick<sup>18</sup>. The existence of the lipolytic and synthetic activities of this enzyme were demonstrated. The estimations of lipase activity were carried out by the method described by Archibald<sup>2</sup>, using as the substrate "Tween 20"<sup>\*</sup> which is a water-soluble mixture polyoxyalkylene derivatives of an ester of 1 mole of lauric acid per mole of sorbitan.

Pure crystalline zinc insulinate<sup>\*\*</sup> in concentrations as high as 100 units per ml. in the digestion mixture had no effect upon the activity of the enzyme.

Tricresol, which is used as a preserv-

pads removed from some of the rats used in the preliminary experiments. In neither the diabetic nor the non-diabetic animals was there any appreciable difference in lipase staining between the side which was injected with insulin and that which received the saline solution.

**Discussion.** The circumstances responsible for the development of insulin lipodystrophy pose a series of baffling questions. For example, why does the condition affect only one out of about every three persons who use insulin? Why does it occur in young people of both sexes but among adults practically only in women? Why do

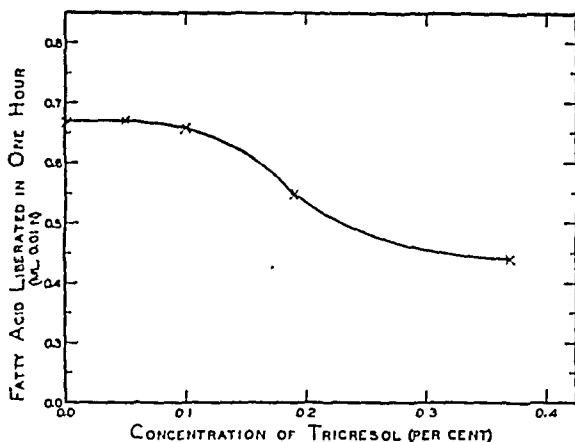


FIG. 4.—Showing the inhibitory effect of tricresol upon the activity of subcutaneous adipose tissue lipase.

ative in commercial insulin in a concentration of 0.1% in the solution of zinc insulin crystals (Toronto) and 0.2% in protamine zinc insulin (Toronto), inhibited the activity of the lipase preparation *in vitro* as is shown in Fig. 4.

Zinc was found to inhibit lipase activity also but the degree of inhibition was less than that caused by the tricresol.

The histochemical demonstration of lipase activity, as described by Comori<sup>10</sup>, was applied to sections of the fat

some diabetics exhibit atrophy and others hypertrophy of the subcutaneous fat? The answers to these and other queries relative to this prevalent complication of insulin therapy are elusive.

Despite the lack of direct evidence implicating an inhibitor of lipase activity in the production of insulin fat atrophy, the possibility that tricresol, or some other constituent of commercial insulin, may play a part should be entertained. In addition to any such fac-

\* Kindly donated by the Atlas Powder Company, Wilmington, Delaware, U. S. A.

\*\* Obtained from the Connaught Laboratories, University of Toronto, through the courtesy of Dr. A. M. Fisher.

tor, a marked individual proclivity to the disorder must be operative.

In the absence of exact knowledge of the causation of this abnormality, wholly rational preventive measures are precluded. The only available treatment consists of varying persistently the sites of injection of the insulin and the use of highly concentrated preparations of insulin. In some cases the depressed regions will fill out, more or less, if they are avoided from the standpoint of the administration of the insulin.

**Summary.** 1. Fat atrophy was not demonstrated at the sites of the repeat-

ed injection of insulin in rats rendered diabetic by means of alloxan.

2. Pure zinc insulin had no effect upon lipase activity *in vitro* at the concentrations employed in the experiments.

3. Tricresol depressed the activity of lipase *in vitro* and, therefore, may be of etiological importance with respect to the insulin fat atrophy which occurs in diabetic patients.

4. Clinical observations are in agreement with the reports of other writers. Approximately 30% of insulin-treated diabetics exhibit the disappearance of subcutaneous fat at the sites of the injection of insulin.

The writers wish to express their appreciation to Dr. J. M. R. Beveridge for valuable assistance with respect to the chemical analyses.

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# PERNICIOUS ANEMIA COMPLICATED BY SYPHILIS

## REPORT OF THREE CASES\*

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It is generally accepted that the response of pernicious anemia to liver therapy may be reduced or completely inhibited by infectious processes occurring as complications. In the standard textbooks of hematology and in the periodical literature, syphilis is usually mentioned as one of the infectious diseases with this capability. Stokes, Beerman, and Ingraham<sup>6</sup> point out, however, that syphilis complicated by pernicious anemia presents a special problem in treatment and that special care should be taken to prevent reactions which may affect the bone marrow adversely. The frequency of pernicious anemia as a complication of syphilis is not great, and few reliable data are available. Foucar and Stokes<sup>2</sup> reporting on a series of 4800 patients with syphilis, found anemia in 25, and of this number 13 were said to be primary anemias. Wilkinson<sup>7</sup>, in a study of 370 patients with pernicious anemia found 6 with syphilis of various types. He stated that although the concurrence of pernicious anemia in syphilis has been noted by others, relatively little attention has been paid to the combination. It is generally agreed that the occurrence of pernicious anemia and syphilis in the same individual is coincidental, and no evidence has appeared to suggest that syphilis can

cause a megaloblastic anemia. A microcytic hypochromic anemia is said to occur as a complication of syphilis and rarely a macrocytic hyperchromic anemia has been reported. The relationship between the latter and syphilis is not at all clear, and one suspects that other complications may be responsible.

Several writers<sup>1,2,7</sup> have reported that the response to liver therapy may be modified when pernicious anemia is complicated by syphilis. Because of the risk of injury to the regenerating bone marrow, Moore<sup>5</sup> states: "In the event of the association of pernicious anemia and late syphilis it is usually desirable to postpone anti-syphilitic treatment until the blood has been brought up to normal by liver therapy. Thereafter, there is no contraindication to administration of arsphenamine or heavy metal in average dosage."

The introduction of penicillin as an anti-syphilitic agent has provided a drug which is not known to have any ill effects on either normal or abnormal bone marrow. The usual course of treatment of syphilis with penicillin is given over a period of 1 or 2 weeks. Thus, it should be possible in appropriate cases to observe the influence of anti-syphilitic treatment on the rate of response of pernicious anemia to

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liver therapy when this complication is present. When heavy metals and arsenicals are used, the duration of treatment is ordinarily so long that it would be difficult to evaluate its effect on the recovery from the anemia.

Since no reports have appeared in the literature concerning the penicillin-treatment of syphilis complicating pernicious anemia, it seemed desirable to report the following cases.

Among the admissions to the Hematology Service of this hospital from January 1, 1947, to July 1, 1948,

duration. Physical examination revealed moderate pallor, and a characteristic, atrophic tongue. The heart was enlarged to the 1-4, and a loud, blowing, diastolic murmur was heard over the aortic area, but best in the fourth left interspace. The erythrocyte count was 2,000,000; hemoglobin, 7.5 gm. %; hematocrit, 24%; mean corpuscular volume, 120 cu microns; mean corpuscular hemoglobin, 37 micro-micrograms; mean corpuscular hemoglobin concentration, 31% and leukocyte count, 10,700. Examination of a smear of sternal marrow revealed a characteristic megaloblastic marrow. The gastric contents contained no free hydrochloric acid after histamine stimulation. The serologic tests for syphilis were negative, although this patient was known to

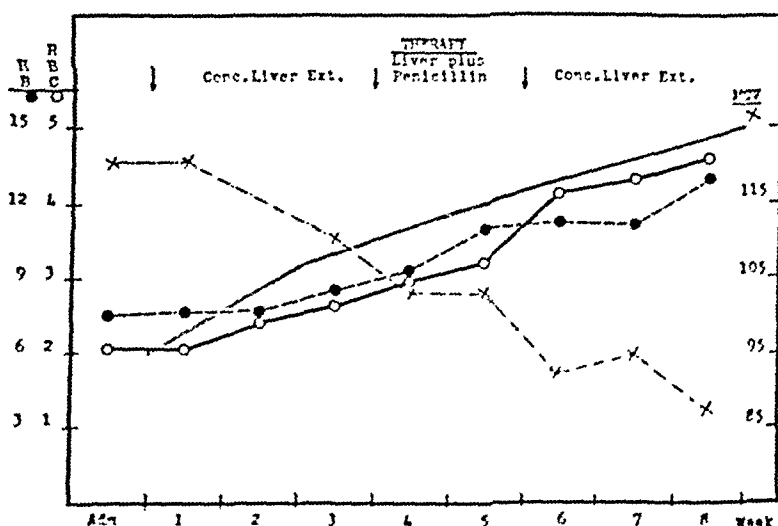


Chart 1.—Case 1, Response to Therapy. ° Red Cell Count. • Hemoglobin. X Mean Corpuscular Volume. — The predicted erythropoietic response, after Isaacs, *et al.*

there were 25 patients with pernicious anemia. Three of these patients had moderately severe anemia, complicated by syphilitic aortic insufficiency, syphilitic aneurysm of the aorta, and late latent, sero-positive syphilis, respectively.

lowing the beginning of combined penicillin-liver extract therapy, the red count increased to 4,200,000, and at the time of discharge from the hospital, 19 days following the start of penicillin, the erythrocyte count was 4,500,000, the hemoglobin was 15 gm., and the hematocrit was 43% (Chart 1).

He had no reaction to penicillin. The average blood counts in each week of treatment are shown in Table 1(A).

CASE 2. E.B., No. 196844, a white male, aged 58, was admitted on Oct. 5, 1947. He gave no history of previous treatment for pernicious anemia, but had been treated for dyspnea, ankle edema and chest pain for 3 months prior to admission. Physical examina-

tion revealed an acutely ill white male with atrophy of the tongue, marked pallor of the skin and mucous membranes, and a lemon-yellow tinge to the skin. A bulging, pulsatile tumor mass was present on the anterior chest in the region of the left 2nd and 3rd inter-spaces. On palpation, a diastolic shock was felt and on auscultation, a systolic bruit was heard over the tumor. The erythrocyte count was 1,300,000; hemoglobin, 5.0 gm.; hematocrit, 14%; the mean corpuscular volume, 138 cu. microns; mean corpuscular hemoglobin, 38 micro micrograms; mean corpuscular hemoglobin concentration, 36%; and leukocyte count, 3500. Examination of marrow obtained from the spinous process of the 3rd

TABLE 1.—LABORATORY DATA AND TREATMENT SCHEDULES IN 3 CASES OF PERNICIOUS ANEMIA COMPLICATED BY SYPHILIS.

| (A) Case 1 |   |                                  |  |                            |                         |
|------------|---|----------------------------------|--|----------------------------|-------------------------|
| Week       | Red Cell Count<br>$\times 10^6/\text{mm}^3$ | Hemoglobin<br>gm. per<br>100 ml. | Mean<br>Corpuscular<br>Volume<br>Cu. Microns | White<br>Cell<br>per c mm. | Treatment               |
| Adm.       | 2.00  | 7.5                              | 120  | 10,600                     | None                    |
| 1          | 2.00  | 7.5                              | 120  | 4,100                      | Liver                   |
| 2          | 2.40  | 7.5                              | —  | —                          | Liver                   |
| 3          | 2.60  | 8.5                              | 110  | —                          | Liver                   |
| 4          | 3.00  | 9.0                              | 103  | —                          | Liver                   |
| 5          | 3.20  | 11.0                             | 103  | 6,100                      | Liver, Penicillin       |
| 6          | 4.10  | 11.0                             | 92   | —                          | Liver, Penicillin       |
| 7          | 4.30  | 11.0                             | 95   | —                          | Liver                   |
| 8          | 4.60  | 13.0                             | 87   | —                          | Liver                   |
| (B) Case 2 |   |                                  |  |                            |                         |
| Adm.       | 1.30  | 5.0                              | 138  | 3,500                      | None                    |
| 1          | 1.70  | 5.5                              | 118  | 6,800                      | Liver                   |
| 2          | 2.00  | 7.0                              | 120  | 6,000                      | Liver                   |
| 3          | 3.00  | 9.0                              | —  | 5,700                      | Liver                   |
| 4          | 3.50  | 11.5                             | 111  | 4,300                      | Liver, Bismuth          |
| 5          | 4.30  | 13.0                             | 93   | —                          | Liver, Bismuth          |
| 6          | 5.60  | 14.0                             | —  | —                          | Liver, Bis., Penicillin |
| 7          | 5.10  | 15.0                             | 88   | —                          | Liver, Bis., Penicillin |
| 8          | 5.50  | 15.0                             | 84   | —                          | Liver, Bismuth          |
| (C) Case 3 |   |                                  |  |                            |                         |
| Adm.       | 1.60  | 6.0                              | 125  | 1,700                      | None                    |
| 1          | 1.80  | 7.0                              | —  | 3,000                      | Liver                   |
| 2          | 2.00  | 7.0                              | 115  | 8,500                      | Liver                   |
| 3          | 2.50  | 9.0                              | 100  | —                          | Liver                   |
| 4          | 2.60  | 9.0                              | —  | —                          | Liver, Penicillin       |
| 5          | 3.10  | 10.5                             | —  | —                          | Liver, Penicillin       |
| 6          | 3.40  | 10.5                             | 95   | —                          | Liver                   |
| 7          | 3.25  | 10.5                             | —  | —                          | Liver                   |
| 8          | 3.24  | 11.0                             | 98   | —                          | Liver, Folic Acid, Iron |
| 9          | 3.26  | 10.5                             | 98   | —                          | Liver, Folic Acid, Iron |
| 10         | 3.30  | 11.0                             | —  | —                          | Liver, Folic Acid, Iron |

lumbar vertebra revealed typical megaloblastic marrow. The gastric secretions contained no free hydrochloric acid after stimulation with histamine. Roentgenologic examination of the chest showed a saccular aneurysm of the arch of the aorta. The serologic tests for syphilis were negative, although the patient was known to have had syphilis at least since 1939 when the aneurysm was first discovered. He had received one inadequate course of anti-syphilitic treatment. The patient was given concentrated liver extract intramuscularly, 15 units daily for 14 days, and then 15 units 3 times a week. During the first 21 days of liver therapy, the red cell count increased to 3,000,000. He was then started on bismuth subsalicylate in oil, 120 mg., intramuscularly once weekly. During the

vious admission, in 1947, a diagnosis of cirrhosis of the liver was also made. He was treated for pernicious anemia at that time, but the red cell count did not exceed 3,500,000 even after several months of continuous liver therapy. He had not taken liver for several months prior to the present admission. On admission, he complained of weakness, pallor and dyspnea of 3 weeks' duration.

Physical examination revealed a moderate pallor of the mucous membranes, atrophy of the tongue, and skin with a lemon-yellow tinge. The erythrocyte count was 1,600,000; hemoglobin, 6.0 gm.; hematocrit, 20%; mean corpuscular volume, 125 cu. microns; mean corpuscular hemoglobin, 37 micro micrograms; mean corpuscular hemoglobin concentration, 30%; and leukocyte count, 1700. A

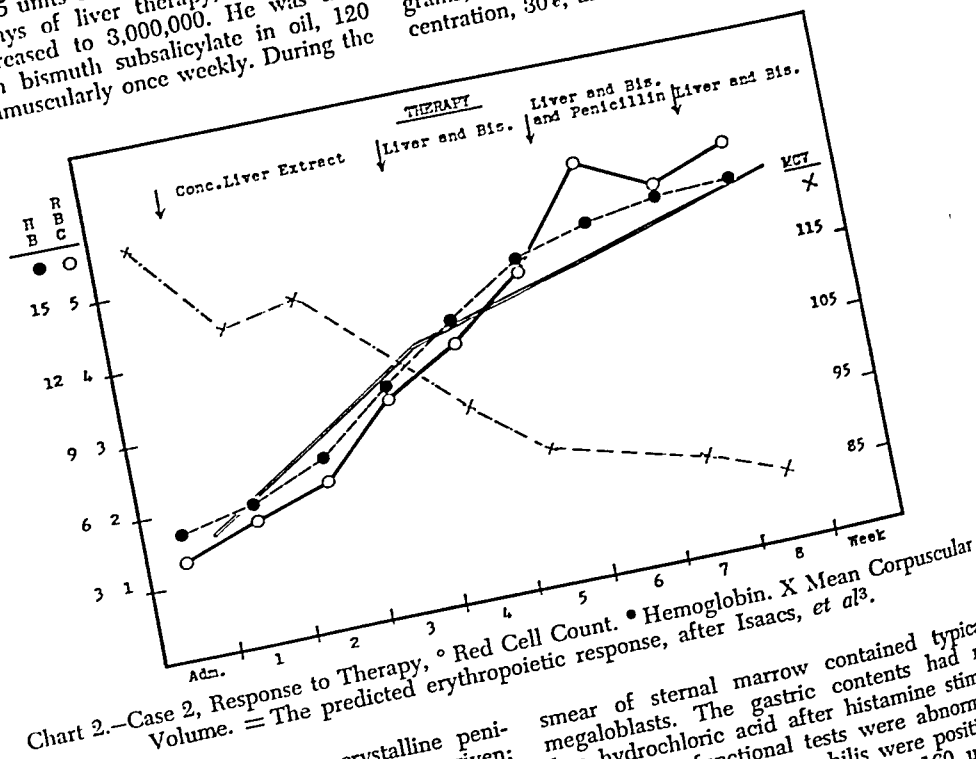


Chart 2.—Case 2, Response to Therapy. • Hemoglobin. X Mean Corpuscular Volume. = The predicted erythropoietic response, after Isaacs, *et al*.<sup>3</sup>

5th week of liver therapy crystalline penicillin, 50,000 units every 3 hours, was given; and continued for 15 days. Upon completion of combined therapy, the erythrocyte count was 5,500,000; hemoglobin, 15.0 gm.; and hematocrit 46%. The maximum reticulocyte response was 28%, on the 7th day of liver therapy (Chart 2).

He had no unfavorable reaction to penicillin. The average blood counts for each week of liver therapy are tabulated in Table 1(B).

CASE 3. D.B., No. 210373, a white male, aged 58, was admitted on June 2, 1948. He was known to have had pernicious anemia and syphilis since 1939. During his last pre-

smear of sternal marrow contained typical megaloblasts. The gastric contents had no free hydrochloric acid after histamine stimulation. Liver functional tests were abnormal. The serologic tests for syphilis were positive: Wassermann, 4 plus; and Kahn, 160 units. The patient was given concentrated liver extract, 15 units intramuscularly, daily for 7 days, then 15 units 3 times weekly. After a period of 21 days of this regimen, the red cell count had increased to 2,500,000. He was then given crystalline penicillin, 75,000 units intramuscularly, every 3 hours for 10 days; a total of 6.0 million units.

Upon completion of this combined therapy, the red blood count was 3,000,000, and one

week later it was 3,400,000 with 10.5 gm. of hemoglobin, and hematocrit 32%. The maximum reticulocyte response was 10% on the 9th day of liver treatment (Chart 3). He had no reaction to penicillin. Since his blood count failed to improve, during the 8th week, folic acid and iron were given, in addition to the concentrated liver extract. After 3 weeks of treatment with all these agents, there was still no change in the blood picture; and it was assumed that the hepatic insufficiency was responsible for the inadequate response to liver therapy. The average blood counts for each week of treatment are shown in Table 1(C).

difficult to estimate the activity of the syphilitic infection in Case 2, but it is a fair assumption that it was active. The aneurysm had increased in size since 1939 when he was given an inadequate course of arsenic.

The availability of penicillin as an anti-syphilitic agent made it possible to give adequate therapy over a brief period of time. It is worthy of note that penicillin did not interfere with the optimal red cell response to liver

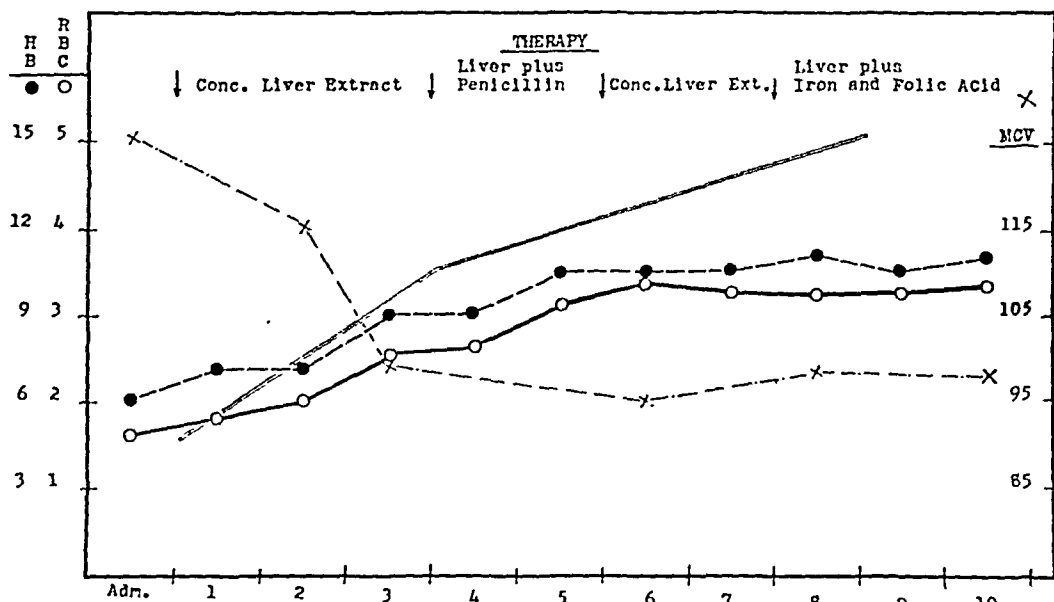


Chart 3.—Case 3, Response to Therapy. ° Red Cell Count. • Hemoglobin. X Mean Corpuscular Volume. — The predicted erythropoietic response, after Isaacs, *et al*.<sup>3</sup>

**Discussion.** A comparison of the hematopoietic response in our patients with the predicted rate of red cell production is of interest and can be seen on the clinical charts. The curves for the predicted erythropoietic response are those described by Isaacs, Bethell, Riddle and Friedman<sup>3</sup>. In Case 2, the observed response closely paralleled the expected one. This was not unexpected, since the observed reticulocytosis, 28%, was greater than the average, 24%, when compared with the standards of Isaacs and Friedman<sup>4</sup>. Their formula, however, is based on a small daily dose of liver extract. It is

extract which this patient displayed. It is also of interest that the aneurysmal region was less painful at the time of discharge.

In Case 1, the red cell regeneration with liver extract was definitely sub-optimal when compared with the standard curve (See Fig. 1). After the initiation of anti-syphilitic therapy, the observed curve showed an upward trend and approximated the theoretical one quite closely. It is difficult to be certain whether this improvement can be attributed solely to the penicillin. The diagnosis of syphilis in this patient was based on the finding of



typical syphilitic aortic insufficiency.

There has been no clinical evidence of activity of this lesion during the 2-year period that this patient was under our observation. In 1946, when pernicious anemia was first diagnosed, the patient was treated with folic acid orally. The maximum reticulocyte response at that time was 13%, or approximately one-half of the usually expected value. The red cell response, however, was equal to, or greater than, the optimal curve throughout the present period of observation of 8 weeks. During the current admission the maximum reticulocyte response with liver therapy was 20%, which is the value predicted by the formula of Isaacs and Friedman<sup>4</sup>. Under these circumstances, one would expect the rate of red cell regeneration to approximate the theoretical curve. Since an active visceral syphilitic infection could impair the response of liver therapy, penicillin was given.

It was gratifying to observe the cessation of the suboptimal red cell response and the occurrence of a normal one.

In Case 3, the anticipated maximum reticulocyte response (according to the Isaacs and Friedman formula), should have been at least 22%, with minimum doses of liver extract. Actually, his maximum value was only 10%, and the peak occurred late, on the 9th day, in spite of adequate doses of liver extract. The exact status of the syphilitic infection was not known in this patient. His serological tests were strongly positive and he had received inadequate treatment with bismuth and arsenic in 1939 only.

Two months after the penicillin therapy the quantitative Kahn reaction was 40 units. No evidence of cardiovascular, visceral or neurosyphilis could be found, and his general physical condition was satisfactory for his age. When it became apparent that the

red cell response to liver extract was also suboptimal, it was assumed that syphilis was responsible. For this reason, anti-syphilitic treatment with penicillin was begun after the 21st day of liver therapy. There appears to have been some improvement in the rate of red cell regeneration which would substantiate our thesis. It is of interest that on a previous admission, the red cell count did not exceed 3,500,000 even after intensive and prolonged liver therapy. However, after the count reached about 3,500,000, and since the completion of the penicillin treatment, there has been no further improvement in the blood picture. No other obvious cause can be found except the unquestionable hepatic insufficiency associated with cirrhosis.

The maximum reticulocyte percentages observed were 20%, 28% and 10% in Cases 1, 2, and 3, respectively. Using the formula of Isaacs and Friedman<sup>4</sup>,  $R = \frac{1 + 0.5 E_o}{82 - 22 E_o}$ , where R is the expected reticulocyte response in per cent, and  $E_o$  is the initial erythrocyte count in millions per cu. mm., the values should have been 19%, 24%, and 22%, respectively. This formula, however is based on data obtained from patients who were given 1 unit of liver extract intramuscularly per day. It has been our experience when the usual dose of liver extract is of the order of 15 units intramuscularly per day during the first week, that the maximum reticulocyte percentage will be greater. We anticipate a reticulocytosis of about 10% for each million that the red cell count is below a normal value of 5 million. Following this calculation, we would expect a maximum reticulocytosis of about 30%, 37%, and 36% in Cases 1, 2 and 3, respectively. On this basis, the reticulocyte responses in these patients were only 1/3 to 2/3 of the usually expected values. Whether this can be assumed

to be a consequence of syphilis, we have no way of knowing; but it is a possibility.

It is well recognized, however, that the reticulocyte response to liver therapy is quite variable, and that it does not always bear a constant relation to the rate of improvement of the erythrocyte count. It is interesting to speculate what the maximum reticulocyte response would have been in these patients if the penicillin had been given at the outset of liver therapy.

In the series of patients with pernicious anemia presented by Wilkinson<sup>7</sup>, the response to combined treatment with extract of hog's stomach and anti-syphilitic drugs was satisfactory in 5 of 6 cases. However, in a report of another group of anemic syphilitics treated with mercury and arsenicals, Foucar and Stokes<sup>2</sup> urged that extreme caution was necessary because of the grave complications which might follow such therapy. In our own patients, the rapid treatment of the syphilis with penicillin caused no unfavorable results.

In Case 2, whose red cell response was practically optimal prior to the administration of penicillin, the rate of regeneration was increased when the antibiotic was given. Certainly, there is no reason to fear that penicillin will have a harmful action on the hemato-

poietic system in patients with pernicious anemia.

Although there is no direct, causal relationship between pernicious anemia and syphilis, it is generally accepted that syphilis can exert an effect on the response to liver therapy. It is probable that this influence is of the same sort that any infective process exerts. It is customary when a patient with pernicious anemia fails to respond adequately to liver extract, first to suspect the quality of the material; and then to search for complicating infections. It is proper to consider syphilis an adequate cause for an unfavorable response in appropriate cases; and rapid treatment with penicillin is indicated.

**Summary and Conclusions.** 1. Three patients with pernicious anemia complicated by syphilis are presented.

2. Penicillin can be administered rapidly to patients with pernicious anemia complicated by late syphilis. There does not appear to be any greater reason to expect adverse reactions from penicillin therapy in patients with pernicious anemia than in patients with late syphilis, generally.

3. It is reasonable to assume that the penicillin should be given as early as possible in the course of the treatment of pernicious anemia complicated by syphilis. If this is done, it seems likely that normal values for the erythropoietic response will be obtained.

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# PREMATURE CALCIFICATION OF THE COSTAL CARTILAGES: ITS FREQUENT ASSOCIATION WITH SYMPTOMS OF NON-ORGANIC ORIGIN

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THE dominant opinion regarding the significance of calcification in the rib cartilages is exemplified by the following statement from a recent textbook of roentgenological diagnosis: "Ossified costal cartilages occur so frequently that they are scarcely worthy of mention"<sup>9</sup>.

That this phenomenon is common is undeniable, although the actual incidence is unknown. To conclude that it has no significance is illogical. Calcification of cartilage is, in the opinion of authorities, an aging process. Why then should it occur in men and women in their twenties and thirties who show no other evidence of premature degeneration? This presentation is an attempt to summarize what is known about calcium deposit in the costal cartilages, to correlate this occurrence with other physical and laboratory findings and to suggest its possible clinical significance.

**ASSOCIATED DISEASES.** What little has been written about the association of calcification of the costal cartilages with disease has been primarily concerned with tuberculosis. A generation ago a number of investigators concluded from statistical studies that patients with apical phthisis showed such calcification at an earlier age and much more frequently than normal subjects<sup>8</sup>. More recently it has been accepted that such a relationship does not exist<sup>3,6</sup>. Huyssen studied the coincidence of calcification in the blood

vessels and that in rib cartilage. Such a wide variation was found that no common factor could be presumed<sup>7</sup>. Kohler<sup>11</sup> demonstrated to his satisfaction that chronic malnutrition was accompanied by increase in costal cartilage calcification, yet Helley<sup>12</sup> could find no association with the diet or the economic background. Falconer<sup>2</sup>, on the basis of postmortem examination, concluded that there is a clear correlation between osteoporosis and hyaline cartilage calcification, a statement possibly accounted for by the fact that both conditions occur frequently in the aged. The same coincidence may account for his finding of frequent anomalies of calcium metabolism, such as gallstones and kidney stones.

From this brief resumé it is apparent that little or no progress has been made in the clinical investigation of this subject.

**MECHANISM OF FORMATION.** In 1939 King<sup>10</sup> made several definite contributions to our knowledge of the anatomy and theoretical significance of premature rib cartilage calcification. Previously, the anatomy textbooks which mentioned the subject at all stated that the calcium was deposited peripherally. King showed, by radiological and histopathological studies, that the calcification is, in the early stages, central and proceeds outward. This has since been confirmed by Hass<sup>4</sup>.

Since most persons deposit some calcium in the rib cartilages by the time

they reach old age there must be some common physiological denominator, over and above the special factors occurring in some younger persons who show this phenomenon. According to King, this basic factor is the movements of respiration. Respiration alone, disregarding the probably greater forces imposed by bodily movement, puts a constant strain on the costal cartilages. In his words, "Every elevation of the ribs involves a stretching of the very strong muscles of the abdominal wall, the strain being spread throughout the anterior thoracic cage by the costal muscles. Every contraction of muscle attached to rib cartilage constitutes a minimal trauma, and can be viewed as a stimulus to physiological change in the direction of increased strength." With trauma there is a reactionary hyperemia, however slight. King states that in very chronic conditions hyperemia causes calcification rather than decalcification, a view which is not generally accepted<sup>1</sup>. King's theory, if correct, might explain why the first costal cartilage invariably calcifies long before the others, since it is from this rib that the whole chest cage is suspended. Confirmatory evidence at present is lacking.

From the purely biochemical standpoint, calcification probably depends on the failure of the mechanism responsible for the maintenance of the intercellular matrix of the cartilage. Hass<sup>4</sup> has made many chemical assays of rib cartilage at various ages and has found that normally the polysaccharide, chondroitin-sulfuric acid, occurs in increased amount from infancy to the fourth decade. It then declines in amount and it is at this time that calcium is deposited in the center of the cartilage, the viability of the cells diminishes, and finally osteoid matrix and bone appear. Hass believes that the chondroitin-sulfuric acid concentration is responsible for maintain-

ing the intercellular matrix, but has expressed no theories about what influences the polysaccharide concentration itself. Hence, as with the clinical studies, we find great gaps in our physiologic and biochemical knowledge of this subject.

In regard to the persons who show the phenomenon of calcification of the rib cartilages at an early age, various predisposing factors have been studied. Some of these, *e.g.*, tuberculosis, have already been mentioned. Dietary deficiencies, possibly of calcium or of vitamin D, have been suggested. The rôle of endocrines in the maturation and aging of cartilage has been systematically and exhaustively studied by the Silberbergs<sup>13</sup> and others<sup>14</sup>. Most of these experiments have been concerned with articular cartilage, but the Silberbergs state that the rib cartilage changes follow the same general pattern. Whether the studies are applicable to man is thrown into some doubt by the fact that the age of the experimental animal on which the hormone acted played an important rôle in determining the mode of reaction of the cartilage. In the young guinea pig, however, androgen and estrogen administration caused premature aging processes in the cartilage, as did parathormone, whereas progesterone had the opposite effect.

**INCIDENCE.** The true incidence of calcification of the rib cartilages is unknown. The best way of obtaining this information in the various age groups would be by Roentgen ray examination of an unselected cross-section of the population. Since this is impossible, we must be content with examination of the people who seek medical attention, either because of symptoms or because of a desire for a "general check-up". The results of such a study will be given, after first considering what other investigators have been able to learn.

Studies were made in Argentina on the basis of chest films of tuberculosis subjects<sup>6</sup>. It should be stated that chest films are rather unsatisfactory for this purpose, unless it is desired to study only the first rib cartilage. Detail below the diaphragm, where the earliest calcifications occur (other than the first rib), is very poorly seen. Of the 1136 patients comprising the material, 41% were between 40 and 50 years of age, 65% older than 30 years. The conclusion drawn was that costal calcification increases with age.

It might be well to recall at this point that calcification of the first costal cartilage occurs so routinely that it

cartilage in 169, and chemical analysis showed clearly that the amount of calcium deposited increases with age. Hass<sup>4</sup> also found this to be true. He showed that the increase begins in the first decade and reaches high values in all cartilage over 50 years of age. It is not, of course, until the calcium content becomes fairly high that it can be roentgenographically detected.

Further evidence that calcification of costal cartilage is a process advancing with age is presented in Fig 1. Five hundred consecutive patients showing this process were grouped according to age incidence by decades. It will be seen that only 29% of these

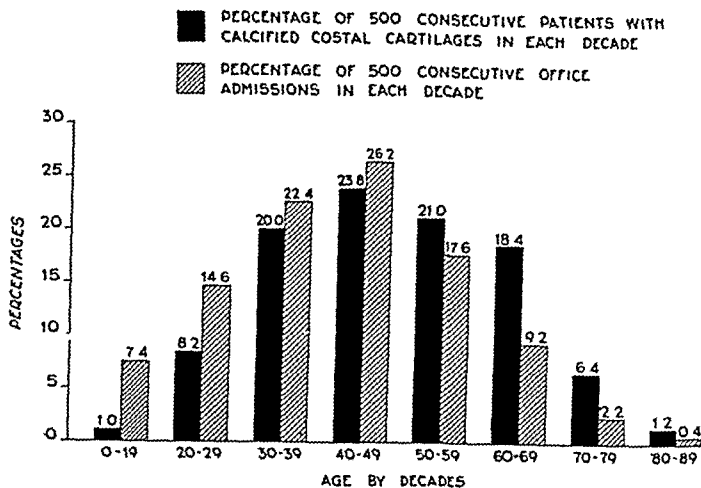


FIG. 1.—Comparison of age incidence in consecutive office admissions and in patients with calcified costal cartilages.

must be regarded as a normal process. According to Rist<sup>12</sup>, it begins at 17 years in the male, 19 years in the female, and is completed at 35 years in the male, and 45 years in the female. It may be completely calcified at a time when none of the other cartilages shows any such change.

One of the two pathological studies that have been reported is that of Falconer, previously referred to. In 200 cases investigated there was deposit of calcium in the rib or tracheobronchial

were under the age of 40. Yet these same younger decades comprised 44% of 500 consecutive admissions to the office. Hence the older age groups constituted a disproportionately large percentage of those with calcification.

All these studies taken together show conclusively that with aging detectable calcification of the costal cartilages is more likely to occur. They do not, however, answer the question of the actual incidence. It would be helpful to know what percentage of the general popu-

lation between the ages of 20 and 29 years exhibits this phenomenon. What percentage of those between 60 and 69 years? If it could be revealed that 1 in 10 shows it at age 20, whereas 7 out of 10 have it at age 60, then its significance in younger persons would be more apparent.

In an attempt to obtain some idea of the actual incidence in the various decades, Roentgen ray films of the right upper abdomen were taken on 300 consecutive patients admitted to the office. This view will detect an appreciable amount of costal cartilage calcification since, excluding the first rib, calcium is first deposited in the lowest cartilages, those which anastomose with each other rather than with the sternum. The deposit is quite equal bilaterally. No details of the patient's record were noted at this time other than age and sex. The films were first

graded according to the presence or absence of significant degrees of calcification, then divided into age groups by decades. Table 1 and Fig. 2 present the results of this tabulation.

It will be seen that the percentage of those with calcium deposit steadily increased with age, with little difference between the male and female incidence. The most marked rise occurred in the fourth decade. The sampling at the age extremes is, of course, too small to have significance. An interesting sidelight of this investigation is that the most marked calcification was not necessarily found in the aged. This coincides with the fact that the amount of calcification in the individual person increases very slowly; little or no difference may be found in films of the same patient 5 to 10 years apart. Those with marked degrees of this phenomenon may acquire it quite early,

TABLE 1.—THE INCIDENCE OF CALCIFICATION OF THE COSTAL CARTILAGES AMONG 300 OFFICE PATIENTS, ACCORDING TO DECADES.

| Age groups by decades           | 10-19 | 20-29 | 30-39 | 40-49 | 50-59 | 60-69 | 70 & over |
|---------------------------------|-------|-------|-------|-------|-------|-------|-----------|
| Number in each decade           | 42    | 62    | 68    | 74    | 31    | 11    |           |
| Male                            | 2     | 12    | 23    | 27    | 28    | 11    | 4         |
| Female                          | 10    | 30    | 39    | 41    | 46    | 20    | 7         |
| Percentage with 0 calcification | 16.7  | 43.5  | 52.9  | 59.4  | 74.3  | 90.9  |           |
| Male %                          | 0     | 16.7  | 34.8  | 59.3  | 53.6  | 72.7  | 100.0     |
| Female %                        | 0     | 16.7  | 48.7  | 48.8  | 60.1  | 75.0  | 85.7      |
| Percentage with 0 extreme calc. | 2.4   | 6.4   | 0     | 5.4   | 6.4   | 18.2  |           |

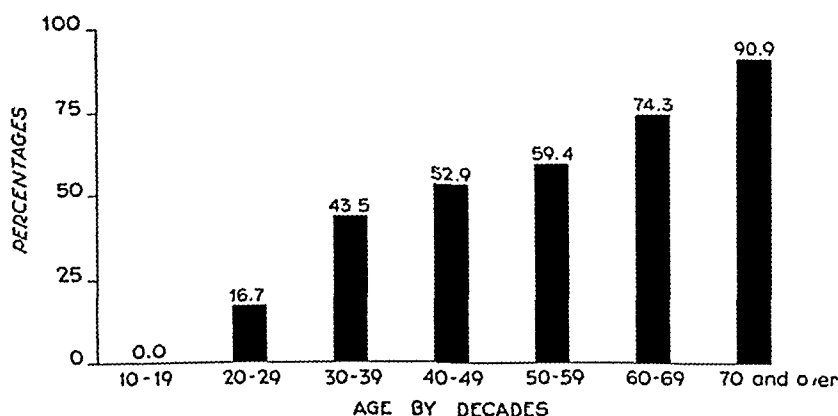


FIG. 2.—Percentage of patients in each decade showing costal cartilage calcification.

then progress but little over many decades. Nevertheless, the figures show that as man gets older he is more and more likely to be subjected to the factors, as yet unknown, which lead to deposit of calcium in the cartilaginous matrix.

**CLINICAL STUDY.** To gain further information about possible associated factors in the younger age groups, the records of a series of office patients under the age of 40 have been examined. Many of these patients were taken from the series of 300 used to determine incidence. Others were discovered by scanning routine gastrointestinal and other abdominal Roentgen ray films. No selection of any kind was exercised other than ascertaining that

number of physicians in our practicing group. With rare exceptions none of us knew, at the time the diagnosis was made, whether the patient did, or did not, have premature costal cartilage calcification. What correlations were found were obtained only after the records had been divided into the 2 groups on the basis of Roentgen-ray evidence.

**Results.** Table 2 presents in summary form some of the data discussed below. Since it has already been shown that calcification is more common with advancing years it is not surprising that the average age in the calcification group was somewhat higher. Although only patients under 40 were selected, the calcification group averaged 32.6

TABLE 2.—SUMMARY OF COMPARATIVE DATA

|                 | Average Age | % Females | % Overweight | % Low B.M.R. | % Menstrual Disorders | Average No. Chief Compl. | % "Functional" or "Indet." |
|-----------------|-------------|-----------|--------------|--------------|-----------------------|--------------------------|----------------------------|
| Calcified Group | 32.6        | 76.6      | 30.0         | 41.1         | 48.6                  | 2.5                      | 77.1                       |
| Control Group   | 28.3        | 68.9      | 12.7         | 43.4         | 14.7                  | 1.3                      | 16.0                       |

the lower rib area was adequately visualized, and that the patient was under the age of 40. These patients were divided into 2 groups. One group, of 158 persons, had definite calcification in the lower costal cartilages. The other, comprising 119 patients, had no radiological evidence of this phenomenon, and was considered as the control group.

In addition to age and sex the following details from the record were noted for comparison between the 2 groups; the complaints, the final chief diagnosis, the state of nutrition, the basal metabolic rate, the blood calcium and history of menstrual disorders in the female patients. The physical examinations and diagnoses were made by a

years as compared with 28.3 years for the controls.

There were slightly more females in the calcification group (76.6%) than in those without calcification (68.9%). This is not a significant difference statistically. The figures do emphasize the well known fact that more women than men seek medical attention.

The few determinations of blood calcium yielded no significant differences. Analyses were made on only 10 patients in the calcification group, the range being 9.6 to 10.6 mg. per 100 cc., all within the normal range. This might be expected in view of the slowness of the calcification process, and the absence of clinical evidence of disturbance of calcium metabolism. In those

of the control group only 2 serum calcium determinations were made. Both were normal.

Again there were found no significant differences between the 2 groups in regard to the basal metabolic rate. There were no thyrotoxic patients in either group and none of the metabolic rates were found to be above plus 10%. If minus 10% is taken as the lower limit of normal (a very questionable figure with the older tables of computation), 41.1% of those having this test per-

The percentage of underweights was approximately the same, while average weights were found considerably more often in the control group. These figures are in contrast to the opinion of Kohler, quoted above, that chronic malnutrition was accompanied by an increase in costal cartilage calcification. However, "malnutrition" and "underweight" are admittedly not synonymous terms in some cases. No significant incidence of anemia was found in either group.

Menstrual disorders were very com-



FIG. 3—Marked costal cartilage calcification in a young woman with multiple complaints of functional origin.

formed in the calcification group were below normal. In the controls 43.4% were below normal.

Each patient was evaluated in regard to nutrition as being overweight, average or underweight on the basis of standard tables prepared from insurance company statistics. It was found that 30% of those in the calcification group were overweight, as compared with only 12.7% of the controls.

mon in younger women with calcification in the costal cartilages. Almost half of them complained of, or admitted on questioning, dysmenorrhea, menorrhagia, gross irregularity of the cycle or scant menstrual bleeding, with no predominance of any one type of disturbance. In contrast, less than 15% of the women in the control group admitted to these complaints.

Early in the study an impression was



gained that the patients later shown to have early calcification in the rib cartilages presented multiple complaints. In order to test this impression the number of chief complaints given by the patient to the examiner on the initial visit were averaged for the 2 groups. The patients in the calcification group were found to have twice as many complaints as those used as controls. A correlated observation was that only 2% of those with calcification reported for examination solely because they desired a "check-up", whereas over 14% in the control group gave this as their reason for coming to the doctor. In other words, more of those with calcification had symptoms which disturbed them, and the symptoms were usually multiple.

The most marked differences came to light with a tabulation of the final chief diagnosis. While more than 60 different diagnoses were recorded by the examiners, 2 predominated overwhelmingly. One was the designation "functional disorder", and included most commonly "psychoneurosis", "anxiety state" and "irritable colon". Four times as many of the calcification group were thus labeled when compared with the controls. The other common diagnosis was the non-committal "indeterminate", meaning that no logical explanation of the patient's symptoms could be found. Seven times as many of the calcification group were thus labeled as compared with the controls. These 2 designations together accounted for 77% of the former group, but only 16% of the latter. The great majority of those with no calcification were found to have a definite organic disorder or were specifically stated to have no disease.

Comparison between various organic diseases yielded no significant differences. In contrast with opinions of the previous generation, as outlined above, pulmonary tuberculosis was found rarely and was actually more frequent in those without calcification. Cholecys-

titis with cholelithiasis was found in very few of either group. Only 1 patient had renal stones. The arthritides, including those in which there is a local calcium deposit, were found to be of significance in the symptomatology of only 2 patients in the calcification series, as compared with 12 patients in the control group.

In summary, patients under 40 who showed calcium deposit in the lower costal cartilages were found to have twice the number of complaints of those who did not. Obesity of moderate or severe degree was over twice as common. In the women the incidence of menstrual disturbances was 3 times as great. And finally, in the opinion of the examiners, the complaints were *not* due to organic disease 5 times as often in the calcification group.

Comment. The question may be raised regarding the validity of our diagnosis of "psychoneurosis" and other designations of functional disorders. Neither my colleagues nor myself are psychiatrists. But we have the keen interest of the present day internist in the psychosomatic viewpoint. We have avoided the pitfall of making the absence of demonstrable organic disease the basis for a diagnosis of "psychoneurosis". Conversely, we have tried to avoid the pitfall of ascribing the patient's symptoms to demonstrable organic disease when, in fact, that organic disease is incidental to the problem. We think that we have made the diagnosis of the functional disorders on positive points in the history, together with evidence on physical examination of nervous instability.

It would appear from the tabulations that a young person with calcification in the costal cartilages is very likely to have a functional disorder. If this can be confirmed by others, the association should be of some significance. Several interpretations, entirely speculative, are possible.

It is possible that the deposit of cal-

cium in the costal cartilages is an effect of the psychoneurosis. In modern psychiatric thinking, emotional tensions can cause not only disturbance of function but, if of long standing, actual organic changes. One may postulate a chronic "alarm" reaction with excessive production of adrenocortical hormones, leading to aging of cartilage through their effect on androgen and estrogens.

It is possible that both the psychoneurosis and the deposit of calcium are on the basis of long standing endocrine disturbance. We already know that psychoneuroses and glandular disorders are frequently related.

It is obvious that experimental work is necessary if either of these hypotheses is to be more than pure speculation. The Silberbergs have done much to show that normal maturation and aging of cartilage in experimental animals can be altered by injection of glandular extracts. It would be much more difficult to show how the psychoneuroses could be fitted into this picture.

**Summary.** Calcification of the costal cartilages is a process which, while presumed to be a matter of aging, is frequently found in young persons.

It is generally thought that this deposit is of no consequence. For this reason, perhaps, very little progress has been made in determining the factors

that cause, or are associated with, the calcification. Association with various organic diseases, such as pulmonary tuberculosis, has been postulated but disproved.

A study of 277 patients under the age of 40 years has been made. Roentgen Ray examinations showed that 158 of these had costal cartilage calcification, while 119 did not. In addition to age and sex, several other details from the case history were tabulated and compared.

Significant differences between those persons who showed calcium in the costal cartilages and those who did not were found in the number of chief complaints, the history of menstrual disorders in the women, the percentage with obesity and the final chief diagnosis. In the former group there were twice the number of complaints, twice the incidence of obesity, 3 times the incidence of menstrual disorders (women alone considered). Most interesting was the fact that the complaints apparently not due to organic disease were 5 times as frequent in the calcification group.

Any interpretation of these differences would at the present time be entirely speculative. It is thought, however, that the answers would be sufficiently interesting and significant to warrant further investigative work.

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# THE VALUE OF LIVER FUNCTION TESTS IN GENERAL HOSPITAL PRACTICE

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In an attempt to determine the practical value of liver function tests in a general hospital, the records of all patients admitted to the Presbyterian-Woman's Hospital of the University of Pittsburgh from September 1, 1946, to September 1, 1948, were reviewed. All patients exhibiting a positive cephalin-cholesterol flocculation test, an elevated bromsulfalein retention, or an elevated icterus were included in this study.

**Methods.** The cephalin-cholesterol flocculation procedure was carried out by the method of Hanger<sup>1</sup>, using Difco cephalin-cholesterol mixture in the absence of light, as recommended by Neefe and Reinhold<sup>4</sup>. This test was read in 24 hours; 1 and 2+ reactions were regarded as being negative, 3 and 4+ reactions as positive. The bromsulfalein test was performed using 5 mg. of dye per kg. of body weight. As noted by Mateer<sup>3</sup>, 4% retention in 45 minutes was taken as the upper limit of normal. In the icterus index test the finding of 10 units or above was considered to be indicative of clinical jaundice.

**Data.** The records of 354 patients with abnormal liver function tests were reviewed. There were 108 cases of non-cardiac cirrhosis, 44 of hepatitis, 32 of common-duct obstruction, 35 of congestive heart failure, 70 of cholecystitis, 4 of leukemia, 7 of lymphosarcoma, 36 of metastatic carcinoma, and 18 with miscellaneous diseases.

**NON-CARDIAC CIRRHOSIS.** Of the patients with non-cardiac cirrhosis, 72 were males and 36 females. Bromsulfalein retention was abnormally high in 71 of the 76 patients in which

this procedure was carried out. In only 22 of 85 members of this group was the cephalin-cholesterol flocculation positive.

In this group 46 patients gave a history of chronic alcoholism, 12 had diabetes mellitus of 5 or more years duration, and in 14 a history of at least one episode of jaundice in the past was obtained. In 36 of the 108 patients in this group no etiologic factor was recognized.

Hepatomegaly was evident in 63 of these cases, 22 had demonstrable ascites, and 6 had splenic enlargement. In 7 cases, jaundice of varying degree was present. Esophageal varices were either demonstrated or a definite history of hemorrhage was recorded in 10 cases.

**CONGESTIVE HEART FAILURE.** In the group of 35 patients with congestive heart failure, 15 were males and 20 females. Nineteen of these had an elevated bromsulfalein retention and in 10 this elevation was above 30%. The cephalin-cholesterol flocculation test was positive in 11 and negative in 21 members of this group. Hepatomegaly was noted in 32, ascites in 11, and jaundice in 5 of these patients.

**HEPATITIS.** Of the 44 patients in this group, males and females were equally divided. The cephalin-cholesterol flocculation test was positive in 39 of the 41 cases in which this test was performed. In 2 cases of arsenical hepatitis a 2+ reaction was obtained. Pain suggestive of gall bladder disease was

prominent as a symptom in 23 members of this group, 33 had an elevation of the icterus index and in 5 hepatic enlargement was demonstrated. Three patients had ascites. In 8 patients an antecedent history of blood or plasma administration was obtained, 4 had marked elevation of the heterophile antibody titer, and in 3 the administration of arsenic was thought to be causative. No patients in this group were troubled by itching. Five patients were surgically explored for the possibility of stone. Two of these surgical patients and one 18 year old girl with serum hepatitis died.

**COMMON DUCT OBSTRUCTION.** In 32 patients with a clinical diagnosis of common duct obstruction, the cephalin-cholesterol test was recorded in 26, and 22 of these were negative. Four patients in this group had a positive test: in 2 of these the obstruction was of approximately 15 months duration, 1 patient died postoperatively of hepatic failure, and in 1 patient liver biopsy at the time of operation revealed no hepatic lesion. The icterus index was elevated in all of these patients. The obstruction of the common bile duct was due to stone or post-surgical stricture in 22 of these cases, 9 had an obstructing carcinoma, and in 1 case the obstruction was evidently due to anomalous enlargement of the right lobe of the liver. In 25 of these patients itching was a prominent symptom.

**CHOLECYSTITIS.** In the 70 patients with cholecystitis, 19 were males and 51 females. The icterus index was elevated in 52 members of this group. In 50 cases the cephalin-cholesterol test was negative. Of the 3 cases in which this test was positive, 1 patient was known to have had acute hepatitis prior to surgery for cholelithiasis. Bromsulfalein retention was noted in 8 members of this group. Two of these had empyema of the gall bladder with liver abscesses, 2 had empyema with

spontaneous rupture of the gall bladder, and 1 with 90% bromsulfalein retention died on the 2nd post-operative day. Gallstones were found by Roentgen-ray examination or by operation in 38 cases; 34 of these were operated upon. The Roentgen-ray findings were positive for stones, and this was confirmed at operation in 16 cases. In 14 cases stones were not found by Roentgen-ray but were disclosed at operation. In 4 cases no preoperative gall bladder Roentgen-ray was obtained. Six patients were found to have empyema of the gall bladder without jaundice. Hepatomegaly was present in 6 cases.

**METASTATIC CARCINOMA.** Of the 36 patients with metastatic carcinoma, 14 had a positive cephalin-cholesterol flocculation test and 22 were negative. Bromsulfalein retention was positive in 21 patients of this group and negative in 4. Of 4 patients with leukemia and hepatomegaly, 2 had bromsulfalein retention and none had a positive cephalin-cholesterol test. Four of 7 patients with lymphosarcoma had a positive cephalin flocculation and 2 had bromsulfalein retention.

**MISCELLANEOUS.** Of 7 patients with pernicious anemia, 5 had positive cephalin-cholesterol flocculation tests, bromsulfalein retention and an elevated icterus. One patient with aplastic anemia had a positive cephalin test, as did 1 case each of ulcerative colitis, silicosis with hepatomegaly, secondary syphilis, amebiasis, nephrosis, and miliary tuberculosis. Bromsulfalein retention was also noted in 1 case of amebiasis, miliary tuberculosis and pulmonary embolism.

**Discussion.** The discrepancy between the bromsulfalein retention and the cephalin flocculation test in non-cardiac cirrhosis is in agreement with the observation that a positive cephalin-cholesterol test requires the presence of an abnormal plasma globu-

lin elaborated by actively damaged hepatic cells<sup>2</sup>. This test does not depend upon the replacement of the hepatic parenchyma by fibrous tissue. The quantitative diminution in the amount of functioning liver tissue is determined by the bromsulfalein procedure. Thus a positive cephalin test requires a qualitative change in liver function, and a positive bromsulfalein test, a quantitative one.

In hepatitis the cephalin-cholesterol test provided consistently accurate evidence of liver damage, except in the presence of arsenical hepatitis. Serum hepatitis occurring in 8 of 44 patients with hepatocellular jaundice emphasizes the frequent occurrence of this disorder. A clinical point worthy of note is that in none of the patients with jaundice due to hepatitis was itching a prominent symptom.

In patients with common duct obstruction the cephalin-cholesterol flocculation test was misleading in only 4 patients, and in these longstanding obstruction or other complications contributed to the situation. Similarly, in only 3 cases of cholecystitis was the cephalin-cholesterol flocculation test positive and 1 of these was known to have an antecedent hepatitis. Failure of Roentgen-ray to reveal stones in 14 of 34 cases with cholelithiasis further

emphasizes the shortcomings of this technique in the problem of gallstones. The absence of jaundice in 6 patients with empyema of the gall bladder contributes to the uncertainty involved in accurately diagnosing this condition preoperatively.

The presence of a positive cephalin test or bromsulfalein retention in a patient suspected to have metastatic carcinoma contributes to the likelihood of this diagnosis. However, the absence of these findings does not exclude this diagnosis.

In pernicious anemia finding 5 of 7 patients with positive liver function tests focuses additional attention on the problems of liver disease in primary anemia.

**Summary.** 1. The records of 354 patients with abnormal liver function tests admitted to a general hospital were reviewed and the diagnostic significance discussed.

2. The value of the bromsulfalein retention test in the detection of cirrhosis and the cephalin test in the diagnosis of hepatitis is emphasized. The absence of the symptom of itching in hepatitis is noted.

3. The value of a negative cephalin-cholesterol test in the differential diagnosis of surgical jaundice, that is, common duct obstruction, is recorded.

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# STUDIES IN PERNICIOUS ANEMIA PATIENTS TREATED WITH LIVER EXTRACT AND FOLIC ACID ANTAGONISTS

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THE efficacy of pteroyl glutamic acid (folic acid) in producing clinical and hematologic remissions in patients with hyperchromic macrocytic anemia (pernicious anemia, sprue, nutritional and pregnancy) has been amply demonstrated since 1945. It has been suggested recently that vitamin B<sub>12</sub> converts free folic acid to the reduced form and that this latter compound is utilized in the production of the erythrocyte maturing factor.<sup>4</sup>

The present investigation was undertaken to study the effect of the administration of synthetic folic acid inhibitors to 5 patients with pernicious anemia treated with adequate doses of liver extract. The two antagonists<sup>3</sup> used in the present experiment are shown on page 198.\*

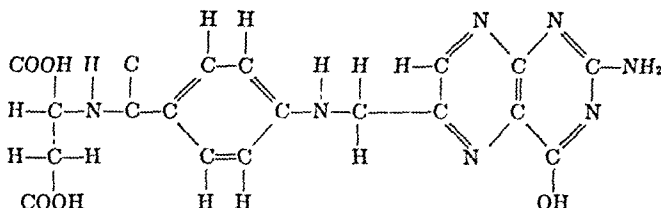
Case Reports, CASE 1. M. S., white male, age 50, was admitted to the Kings County

Hospital complaining of weakness for 1 year and vomiting and diarrhea for the past 3 weeks. There was soreness of the tongue about 6 months previously and vague numbness and tingling of the hands and feet. A yellowish pallor of the skin had been present for the past month. Physical examination revealed an icteric tint to the sclerae. The tongue was red and smooth. The spleen was felt 2 cm. below the left costal border. Vibratory sensation was reduced in the lower extremities. The blood studies are shown in Fig. 1. Other laboratory data were: No free hydrochloric acid in gastric juice after histamine; Roentgen-ray studies of gastro-intestinal tract negative; stools negative for occult blood; blood sugar 95 mg.; N.P.N. 27 mg., icterus index 12; bone marrow megaloblastic.

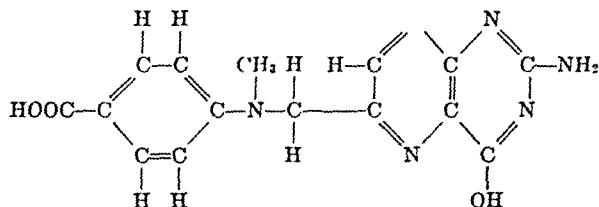
The patient was given an experimental liver fraction which was followed by a satisfactory reticulocyte response and rise in hemoglobin and red cells. The tongue became less painful and the diarrhea subsided. There was improvement in the appetite and general well-being. After 20 days the blood count fell to near pre-treatment levels. The bone marrow was again megaloblastic. The patient was treated with 5 units of liver extract, intra-

\* Supplied by Lederle Laboratories Division of American Cyanamide Company, Pearl River, N. Y.

## PTEROYL ASPARTIC ACID (AN-FOL-R)



## METHYL PTEROIC ACID (MET-FOL-B)



muscularly, daily, and on subsequent days as indicated in Fig. 1. Simultaneously he received 40 mg. and then 200 mg. of Met-Fol-B daily. During the period of the smaller doses of the inhibitor there was a slight rise in reticulocytes (7.1%) and increase in hemoglobin and red cells. After the dose of Met-Fol-B was raised to 200 mg. a day the red blood cells did not rise for a period of 1 month, even though he received 5 units of

liver extract every 4 days. Bone marrow examination after 4 weeks of combined liver extract and Met-Fol-B treatment showed less than 5%.

During this period the patient was poor and complained of weakness and fatigue. Following the discontinuance of Met-Fol-B he received liver extract at the same intervals (5 units/4 days). Although no reticulocytosis followed, the hemoglobin and red cells rose slowly and

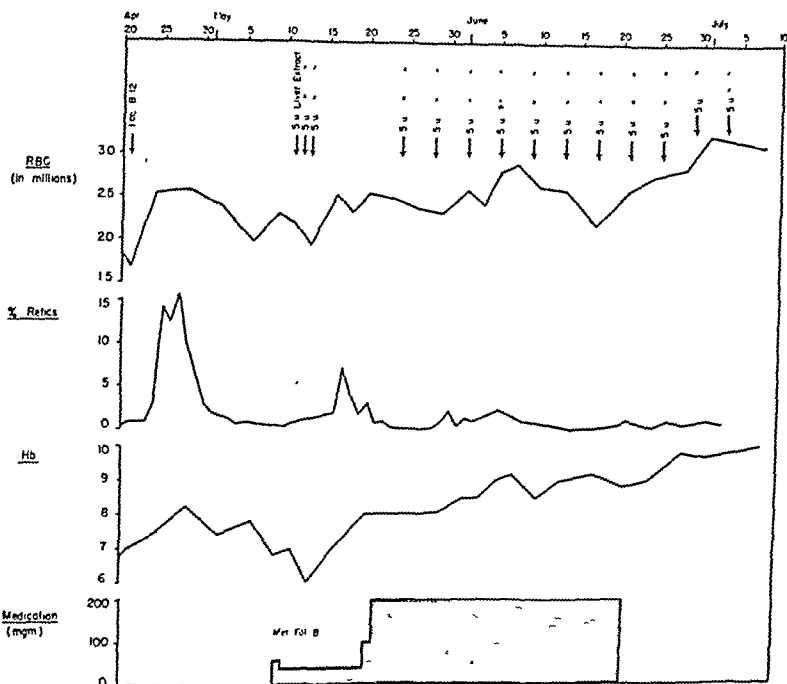


FIG. 1.—HEMATOLOGIC DATA IN CASE 1.

the clinical condition of the patient gradually improved.

CASE 2. J. W., white male, age 76, was admitted to the Kings County Hospital because of severe burning epigastric pain. He received intermittent liver therapy for pernicious anemia for 19 years, but had no treatment for the 4 months immediately preceding admission to the hospital. Examination showed a sick old man, pale and undernourished, with a yellow discoloration to the sclerae and skin. The tongue was smooth at the edges. There was absence of vibratory sensation in the lower extremities. Hemoglobin and red cell studies are presented in Fig. 2. Additional laboratory data showed large numbers of white blood cells in the urine; Roentgen-ray examination of gastro-intestinal tract negative; no occult blood in stools; blood sugar 110 mg.; urea N. 18 mg., icterus index 8; cephalin flocculation 3 plus; bone marrow megaloblastic.

The patient was transfused with 500 cc. of blood on each of 2 successive days. This resulted in clinical improvement, with an increase of hemoglobin and red cells to 6.0 gm. and 1.52 million, respectively. He was given 10 units of liver extract once and 40 mg. of Met-Fol-B daily. A reticulocyte response of 6.7% occurred on the 5th day, but there was a gradual fall in the hemoglobin and red cells to 4.0 gm. and 1.37 million. A transfusion of 500 cc. of blood was administered. The following day he was again given 10 units of liver extract and 40 mg. of Met-Fol-B

daily. After 9 days, 10 units of liver extract were injected. The dose was repeated after the same period. Thereafter, 5 units of liver extract were given every 4 days, and 60 mg. of Met-Fol-B were administered. The observation covered 41 days, and during this time the hemoglobin and red cells remained stationary. No reticulocytosis occurred. Bone marrow contained 5 to 15% megaloblasts. The patient showed no clinical improvement. During the last 10 days of the study he complained of weakness, tiredness, and appeared ill. After the drug was discontinued 5 units of liver extract were injected intramuscularly every 4 days. No reticulocytes were found during the following 20 days. The hemoglobin and red cells rose very slightly and the clinical improvement was also slow. He did not reach a normal hemoglobin and red cell level 2 months after cessation of anti-folic acid therapy.

CASE 3. M. M., white female, age 64, was admitted to the Kings County Hospital because of weakness of several weeks' duration. She had symptoms of mild cardiac decompensation for 7 years, and was treated with digitalis. Occasional episodes of constipation occurred intermittently. The day before admission to the hospital the patient received an injection of 10 units of liver extract and 100 mg. of B complex (containing 10 units of liver extract). Physical examination revealed a pale, but not acutely ill, aged female. The tongue was smooth at the edges. The liver was felt 2 cm. below the right costal border.

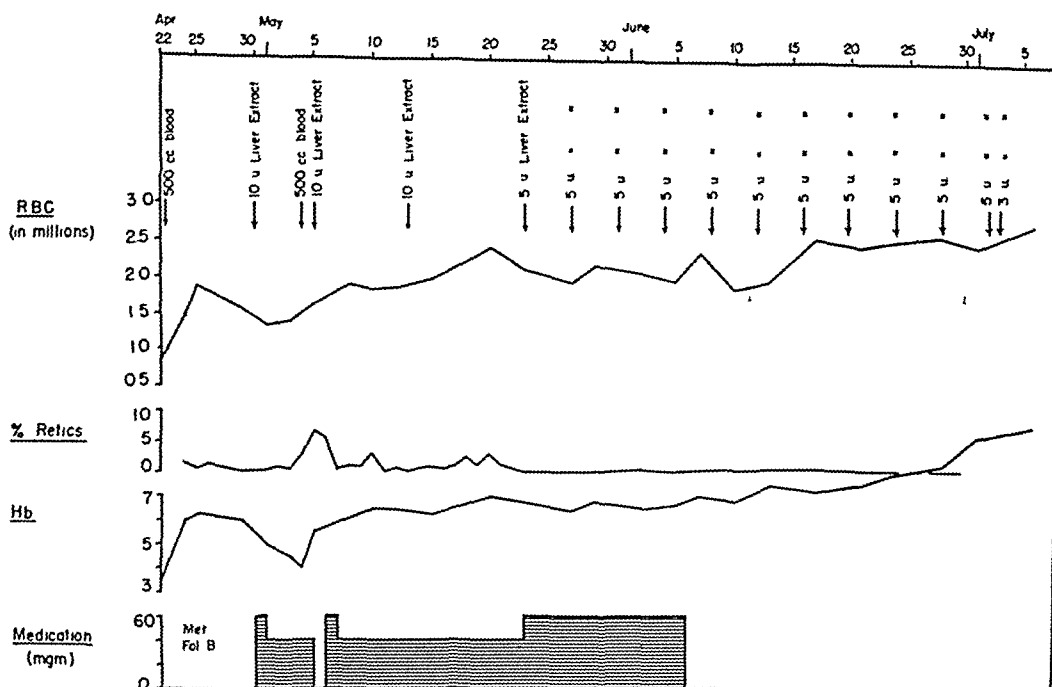


FIG. 2.—HEMATOLOGIC DATA IN CASE 2.



The tip of the spleen was palpable. Neurological status was normal. Peripheral blood studies are found in Fig. 3. Other pertinent laboratory data were: blood sugar 88 mg.; urea 40 mg.; total protein 7.1 gm.; icterus index 10; no free hydrochloric acid in gastric juice after histamine; Roentgen-ray examination of gastro-intestinal tract negative; bone marrow megaloblastic.

Three days after the injection of liver extract (10 units) and B complex (100 mg.) the patient was given 40 mg. of Met-Fol-B intra-muscularly, daily, for 4 days. There was

reticulocytosis, slow rise in hemoglobin and red cells and gradual improvement in the well-being of the patient.

CASE 4. M. W., white female, age 81, was admitted to the Kings County Hospital because of weakness, vomiting and epigastric pain. She was a patient at the hospital 3 years previously, at which time a diagnosis of pernicious anemia was established. Parenteral liver extract was administered up to 6 months before the present admission. On the 4 days prior to her entry to the hospital she received 30 units of liver extract from her local physi-

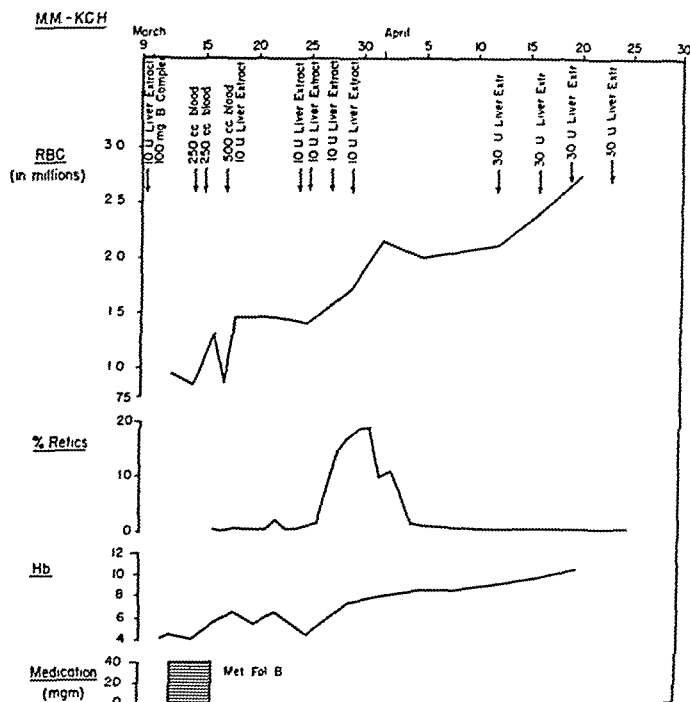


FIG. 3.—HEMATOLOGIC DATA IN CASE 3.

no reticulocyte response and the red cells fell to below 1 million. The patient appeared critically ill and 2 transfusions of 250 cc. of blood were administered on 2 successive days. Eight days after the first liver extract injection, and 1 day after Met-Fol-B was discontinued (total of 160 gm./4 days) the patient received 500 cc. of blood and 10 units of liver extract. During the following there was no reticulocyte response and the red cells remained stationary (except for the rise following transfusion). Three marrow studies during this period showed a marked megaloblastosis (up to 34%). The patient continued to be weak, somnolent and languid. She was then given 10 units of liver extract on 2 successive days. This was followed by a weak

cian, a total of 120 units. On admission to the hospital the physical examination revealed no remarkable findings. The hematologic findings are recorded in Fig. 4. The bone marrow showed 2% megaloblasts. Other laboratory data were: total protein 5.1 gm. (albumin 2.7 and globulin 2.4); blood urea 50 mg.; blood sugar 83 mg., icterus index 6; cephalin flocculation 2 plus; prothrombin time 14 secs. (control 13.2). The reticulocytes were 27.1% on the day of admission and fell to less than 1% 11 days later. On the 5th day after the first injection of liver extract 100 mg. of Met-Fol-B were administered intra-muscularly for 16 days. At the end of this period the medication was discontinued because the patient became weak, unable to

walk, and disoriented. Pallor developed and her condition was poor. During this time there was a slight rise of hemoglobin and red cells from 6.0 and 1.3 million to 8.0 gm. and 1.93 million. The bone marrow contained less than 1% megaloblasts. After the Met-Fol-B was discontinued there was a gradual improvement in the patient's well-being, but she was unable to get out of bed to walk. For the first 15 days the blood count did not rise. Thereafter, the hemoglobin and red cells slowly increased to 9.0 gm. and 2.34 million (12 days later). With the administration of liver extract there was a slow but steady increase in hemoglobin and red cells so that at the time of discharge they were 12.5 gm. and 3.33 million. There was an absence of reticulocyte response other than the initial one noted on admission to the hospital.

were: No free hydrochloric acid in gastric juice after histamine; blood sugar 79 mg.; urea 43 mg.; Roentgen-ray examination of gastro-intestinal tract negative; stools contained no occult blood; marrow contained 2% megaloblasts.

Two days after the patient received the injection of liver extract (10 units) he was given 20 mg. of An-Fol-R intra-muscularly, and sulfadiazine, 4 gm. orally, daily. The medication was given for 12 days. During this period satisfactory reticulocytosis occurred, but no increase in hemoglobin and red cells took place. The patient appeared clinically poor and complained of weakness. A bone marrow aspiration disclosed 16% megaloblasts. Without further treatment for 15 days the blood picture and the clinical condition remained unchanged. A subsequent

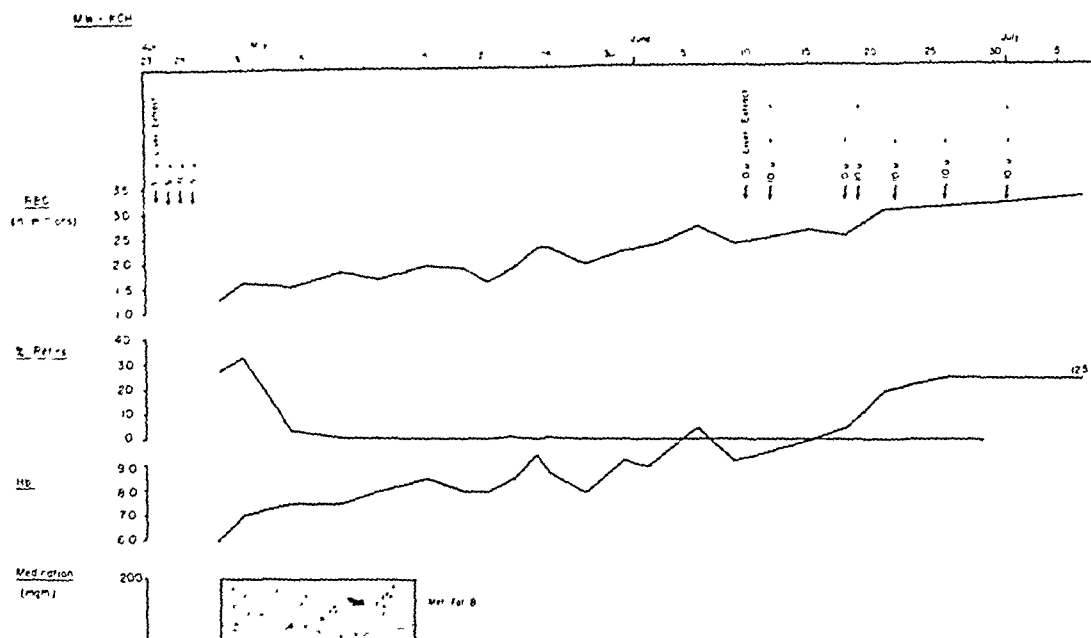


FIG. 4.—HEMATOLOGIC DATA IN CASE 4.

CASE 5. K. M., white male, age 59, was admitted to the Kings County Hospital because of weakness and pallor of 2 years' duration. He had intermittent treatment with liver injections, lexitron and vitamins during this period. Three weeks before admission to the hospital his tongue became red, sore and "burned like fire". He complained also of numbness and tingling of his hands and feet. One day before admission to the hospital he received an injection of liver extract (10 units) from his local physician. Physical examination showed a tongue with atrophic mucosa. There was absence of vibratory sensation in both lower extremities up to the iliac crests. The hemoglobin and red cell studies are shown in Fig. 5. Other laboratory data

injection of 30 units of liver extract for 3 days was followed by a satisfactory rise in hemoglobin and red cells. Reticulocyte studies were not done as the patient left the hospital. There was a marked improvement in general well-being.

**Discussion.** The approach to the problem was not uniform because some of the patients received injections of liver extract before entering the hospital. It was felt desirable to study the effect of the inhibitors in these cases in which a variable period of stimulation had already occurred. This is demon-

strated in Cases 3, 4, and 5. Cases 1, 2, 3 and 4 indicate that the dose of folic acid antagonist necessary to prevent reticulocytosis and increase in hemoglobin and red cells varies in different patients. In Case 1, 40 mg. of Met-Fol-B daily had only a partial effect, whereas 200 mg./day resulted in no reticulocyte response and a stationary blood picture for one month. After discontinuance of Met-Fol-B the further administration of liver extract was followed by a slow rise in hemoglobin and red cells but no reticulocytosis occurred. Case 2 also had a weak reticu-

After the administration of 20 units of liver extract there was complete absence of reticulocyte response and a fall in the hemoglobin and red cells, with only 40 mg. of Met-Fol-B for 4 days. Injection of 10 units of liver extract was followed by no change in hemoglobin, red cells, or reticulocytes. The administration of 10 units of liver extract on each of 2 successive days 1 week later resulted in a slow increase in hemoglobin and red cells and a very poor reticulocyte response. Case 4 came under observation when already enjoying a satisfactory reticulocytosis. The

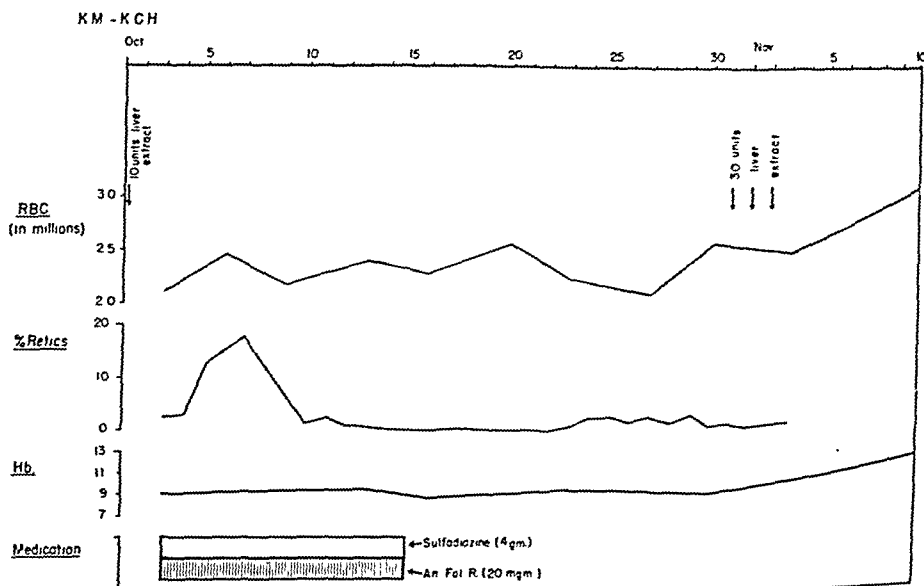


FIG. 5.—HEMATOLOGIC DATA IN CASE 5.

locyte response, with an actual fall in hemoglobin and red cells, necessitating transfusion when given 40 mg. of Met-Fol-B daily and 10 units of liver extract. Adequate liver therapy and 60 mg. of antagonist per day were followed by no reticulocytes or change in peripheral blood count. After Met-Fol-B was discontinued and repeated liver extract injections, there was a slow rise in the red cells and hemoglobin, but no reticulocyte response was ever evoked. Patient 3 had a similar course.

administration of 200 mg. of Met-Fol-B for 16 days had no apparent effect on the reticulocytes, but the hemoglobin and red cell count remained practically unchanged. Fifteen days after the drug was discontinued the blood count was stationary and then began to rise slowly. Case 5 was treated with An-Fol-R, a less potent folic acid antagonist than Met-Fol-B.<sup>1</sup> The sulfadiazine was administered to prevent the liberation of folic acid in the small intestines.<sup>2</sup> Although a satisfactory reticulocyte re-

sponse occurred following 10 units of liver extract, no change in hemoglobin and red cells took place. Cases 2, 3, and 5 were of special interest in that these patients showed marked megaloblastosis after treatment with the folic acid antagonists, even though they received adequate liver therapy. All the patients uniformly appeared ill, and complained of weakness, fatigue and somnolence while receiving either antagonist. This was particularly evident in those treated with Met-Fol-B. It was also apparent that the drug had a continued effect, since after discontinuance the patients felt poorly, had no reticulocyte reactions, and no clinical improvements were noted. The previous administration of large doses of liver (120 units in Case 4) was inactivated, since after Met-Fol-B treatment was stopped no change in hemoglobin and red cells took place. Patient 3 received a total of 30 units of liver extract with no response one week after discontinuance of Met-Fol-B, apparently due to prolonged inactivation by 160 mg. of the drug.

Recently Jacobson and Good have demonstrated that the hematopoietic activity of folic acid can be enhanced by incubation of the vitamin with an enzyme obtained from fresh milk and cream.<sup>1</sup> The enzyme has no potency when given alone. Vitamin B<sub>12</sub> how-

ever, appears to act without the simultaneous administration of folic acid but there may be enough of the latter vitamin in the tissues to be activated.<sup>6</sup> The relationship of B<sub>12</sub> to the cream enzyme and the recently prepared animal protein factor<sup>5</sup> remains to be clarified. The authors are at present investigating the effect of the simultaneous administration of vitamin B<sub>12</sub> and folic acid antagonist to patients with pernicious anemia in relapse.

**Conclusion.** The lack of hematologic response in patients with pernicious anemia treated with adequate doses of liver extract and a folic acid antagonist suggests that pteroyl glutamic acid is necessary for the production of red blood cells.

Since the completion of the above report a patient with pernicious anemia in relapse was treated with 200 mg. of Met-Fol-B daily for 14 days. On the 3d and 11th days of therapy he was given 10 and 15 gamma of vitamin B<sub>12</sub><sup>\*</sup> respectively and 5 mg. of a-methopterin (4-amino 10-methyl pteroyl glutamic acid) intra-muscularly. There was no clinical remission or reticulocyte response; the hemoglobin, red cell and white cell counts did not rise; and 4 sternal aspirations done during the period of observation revealed a megaloblastosis of 11 to 23%.

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\* Supplied by Merck and Co., Rahway, N. J.

# THE PAIN REACTION THRESHOLD IN THE MENOPAUSAL SYNDROME

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It is becoming increasingly apparent that the emotional symptoms and the majority of the manifestations of disturbed autonomic nervous system function associated with the "menopausal syndrome" are of psychologic rather than endocrine origin.<sup>4,9,10,15</sup> Comprehensive psychiatric studies<sup>5,7,11,13</sup> have indicated clearly that with few exceptions these symptoms are the result of pre-existing personality and emotional disorders which come into focus or for various reasons are exaggerated at the time of the climacteric. The endocrine changes accompanying this latter normal physiologic phenomenon have been shown to produce the cessation of menstruation, alteration of secondary sexual characteristics, atrophy of the skin and vulva, osteoporosis, and possibly some of the hot flashes. That arterial hypertension might also result has been refuted by Taylor, Corcoran, and Page.<sup>14</sup> Factual evidence that hypo-ovarianism can cause significant changes in emotional reactions is lacking. The lack of correlation between menopausal symptoms and excretion of gonadotropic and estrogenic hormones has been noted by Geist and Mintz.<sup>6</sup>

It is inconsistent that the diagnosis of "menopausal syndrome" is so often made on the basis of emotional and autonomic symptoms alone, regardless of age or relationship of symptoms to proved endocrine changes. In our experience, more careful psychiatric evaluation with particular attention to psy-

chodynamic considerations will establish the majority of these problems as psychoneurotic reactions resulting from environmental or interpersonal factors quite apart from the menopause. The similarity between the symptoms of the "menopausal syndrome" and some of the psychoneurotic reactions has been noted by others.<sup>7,9,10,15</sup>

Previous experimental studies have shown that as a group psychoneurotic patients, especially those with anxiety tension states or neurocirculatory asthenia, have a significantly lower pain reaction threshold than do normal subjects or control "non-psychoneurotic" patients.<sup>1,2,3,12</sup>

It became of interest to determine the relationship of pain perception and reaction thresholds of menopausal patients to these thresholds of normal and psychoneurotic subjects.

**Method and Experimental Data.** The pain perception and reaction thresholds were determined with Hardy-Wolff-Goodell radiation apparatus, which has been described in detail elsewhere.<sup>8,12</sup> Briefly, this apparatus is a device for delivering a controlled, measured amount of radiant heat to the skin of the subject being tested so that the levels at which he perceives and reacts to pain can be determined. By using a pair of lenses the light from a rheostatically controlled 500 Watt incandescent lamp was concentrated at the testing orifice of the apparatus. The exposure time was kept constant at 3 seconds by an electrically timed shutter, and each subject was repeatedly tested at varying intensities of stimulation.

Statistical validity of the results was tested by determining the critical ratio of the  $\bar{z}$

means. Valuable assistance with this phase was rendered by Dr. J. A. E. Eyster, Professor of Physiology, University of Wisconsin.

The subjects were all ambulatory patients in the State of Wisconsin General Hospital. The control group consisted of 44 adult "non-neurotic" female patients. Their illnesses were such as are not commonly judged to be of psychosomatic or psychogenic origin. Diagnoses common in this group were diabetes, osteoarthritis, malignancy, rheumatic heart disease, and cholelithiasis.

The experimental group consisted of 22 women, ranging in age from 27 to 53 years, in whom a diagnosis of menopausal syndrome had been made. Six patients of this group had been castrated surgically. A third group consisted of 41 adult females in whom a diagnosis of psychoneurosis, mostly anxiety tension type, had been made.

Patients included in the menopause group were chosen solely on the basis of their having been given a primary diagnosis of menopausal syndrome. None was psychotic. When these patients were submitted to a more detailed psychiatric appraisal, it became apparent that the majority of them had what would have been diagnosed as psychoneurosis had they not been in the "menopause age" or castrated surgically.

**Results** (See Table 1). The average pain perception threshold for the 44 "non-neurotic" females was .342 gm. cal./sec./cm<sup>2</sup>. The average pain perception threshold for the 22 menopause patients was .345 gm. cal./sec./cm<sup>2</sup>. There is no significant difference between these figures.

TABLE 1.—PAIN PERCEPTION AND PAIN REACTION THRESHOLDS.

| Group                                   | Average Pain Perception Threshold | Average Pain Reaction Threshold |
|---|-----------------------------------|---------------------------------|
| 44<br>"Non-neurotic"<br>Female Patients | .342                              | .497                            |
| 22<br>Patients with Menopausal Syndrome | .345                              | .436                            |
| 41<br>Female<br>Psychoneurotics         | .340                              | .421                            |

\* Gram Calories per second per sq. cm.

The average pain reaction threshold for the 44 "non-neurotic" women was

.497 gm. cal./sec./cm<sup>2</sup>, whereas for the 22 menopause patients it was .436, and for the 41 female "psychoneurotics" it was .421.

The critical ratio for the mean of the reaction levels of 44 non-neurotics compared to 22 menopause patients was 3.23, indicating that these results would occur by chance less than twice in a thousand trials.

The critical ratio of the mean reaction threshold of 44 non-neurotic females compared to 41 neurotic females was 5.3 indicating that these figures would occur by chance less than once in 10,000 trials.

The critical ratio of the averages of the menopausal group compared to the female neurotic group is less than 1, indicating that these figures are not significantly different when analyzed statistically.

In an earlier paper,<sup>12</sup> it was shown that the fusion of a subject's perception and reaction thresholds was strong evidence for the existence of a significant emotional disturbance; or, when the reaction level was so low as to be identical with the perception level, the subject was most likely suffering from a definite emotional disorder. In the group of 22 "menopause" patients, 5 (23%) showed a fusion of perception and reaction thresholds. None of the 44 "non-neurotic" patients showed this phenomenon.

**Summary.** A group of 22 patients diagnosed as having menopausal syndrome was found to have an average pain reaction threshold significantly lower than that found in a control group of 44 "non-neurotic" adult female patients. The pain reaction threshold of the menopause group was similar to that of a group of psychoneurotic patients.

**Conclusion.** Pain perception and pain reaction thresholds of menopausal women closely resemble those of psychoneurotic patients.

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# PAIN REACTION THRESHOLDS IN PATIENTS WITH PEPTIC ULCER

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THE emotional features frequently found in patients with peptic ulcer are well known. There is an increasing volume of literature which indicates the importance of emotional disturbances in the pathogenesis and course of peptic ulcer. Many clinicians feel that psychotherapy is the most effective means of treatment. The dictum "treat the entire patient, not *only* his ulcer" is generally accepted.

In such patients, then, it becomes important to recognize the existence of and to determine the nature of abnormal emotional reactions. For the most part, these observations depend upon clinical study. Occasionally, laboratory aids can contribute information helpful to accomplishing a more complete evaluation of a patient. Chapman *et al.*,<sup>3</sup> and Schilling and Musser<sup>5</sup> have shown that the pain reaction threshold for a group of psychoneurotic patients was significantly lower than in the control group. The pain perception thresholds were identical. Since it is widely recognized that patients with peptic ulcer have significant emotional problems, it was of interest to determine if the pain perception and pain reaction thresholds of ulcer patients were comparable to "non-neurotic" patients or to psychoneurotic patients.

**Method and Experimental Data.** The pain perception and pain reaction thresholds were determined with a

Hardy-Wolff-Goodell radiation apparatus.<sup>4</sup> The technique used has been described in detail previously.<sup>5</sup> Briefly, this apparatus is a device for delivering a controlled, measured amount of heat stimulation to the skin of the subject so that the levels at which he perceives and reacts to pain can be determined. By using a pair of lenses the light from a rheostatically controlled 500 Watt incandescent lamp was concentrated at the testing orifice of the apparatus. The exposure time was kept constant at 3 seconds by an electrically timed shutter, and each subject was repeatedly tested at varying intensities of stimulation.

The statistical analyses were made by the method of determining the critical ratio of the 2 means. Valuable assistance with this phase was given by Dr. J. A. E. Eyster, Professor of Physiology.

The subjects were all ambulatory patients in the State of Wisconsin General Hospital. The control group consisted of 53 "non-neurotic" male patients, that is, patients whose illnesses were judged to be "organic". The diagnoses included various forms of malignancy, diabetes, osteoarthritis, anemias, and so on. The experimental group consisted of 23 men having active peptic ulcers, 18 duodenal and 5 gastric. The average pain perception thresholds for the control group was .369 gm.



cal./sec./cm.<sup>2</sup>\* The average pain perception threshold for the peptic ulcer group was .367 gm. cal./sec./cm.<sup>2</sup>. These figures are not significantly different.

The average pain reaction threshold for the control group was .529 gm. cal./sec./cm.<sup>2</sup>, whereas the average pain reaction threshold for the peptic ulcer group was .471 gm. cal./sec./cm.<sup>2</sup>. The critical ratio of these 2 means would occur by chance less than once in a thousand trials.

In an earlier paper<sup>5</sup> it was shown that fusion of subjects' perception and reaction thresholds was strong evidence for the existence of a significant emotional disturbance. Stated differently, when the reaction level was so low as to be the same as the pain perception level the subject was most likely suffering from a definite emotional disorder.

In the group of 23 men with ulcer,

- \* Gram calories per second per sq. cm.

5 (22%) showed a fusion of perception and reaction. In the group of 53 "non-neurotic" male patients, none showed a fusion of perception and reaction.

Discussion. These studies demonstrate that men having an active peptic ulcer require essentially the same amount of stimulus to perceive cutaneous pain as do "non-neurotic" male control patients. They differ from the control subjects in that they require significantly less stimulation to cause pain reaction (a wince or motor withdrawal). In this regard they closely resemble psychoneurotic patients.

Summary. As a group, 23 men with peptic ulcer showed a significantly lower pain reaction threshold than that found in a control group of 53 "non-neurotic" male patients.

Conclusion. Pain perception and pain reaction thresholds of peptic ulcer patients are similar to those of psychoneurotic patients.

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# RECURRENT MIGRAINOID HEADACHES ASSOCIATED WITH SPONTANEOUS HYPOGLYCEMIA\*

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In 1935 Gray and Burtne<sup>8</sup> described headaches of a migrainoid character that were associated with hypoglycemia. While their criteria for hypoglycemia (60 to 90 mg. per 100 cc.) might be questioned by some<sup>2</sup>, there seemed to be a definite connection between the blood sugar level and the onset of the attack. Frequent feedings of carbohydrate containing foods prevented the attacks, while they could be precipitated by hypoglycemia induced with insulin. Of the 38 patients reported, 22 were described as having "true migraine".

Little attention was given to this paper, though Girard and Colleson<sup>7</sup> reported an additional series of cases with unilateral headache associated with hypoglycemia, and it has recently been quoted in one monograph on headaches<sup>12</sup>. Also Porges<sup>13</sup> and later Földes<sup>9</sup> reported low carbohydrate and, or, high protein diets as being of benefit in migraine, but apparently did not associate this with accepted methods of treating spontaneous hypoglycemia<sup>3,15</sup>.

In spite of the fact that the syndrome associated with temporary, and frequently mild, hypoglycemia, attracted but little interest a number of studies have been done on the more serious aspects of prolonged hypoglycemia<sup>1,4,5,11</sup>.

Two cases of migraine were reportedly relieved by induced hypoglycemia<sup>14</sup>. A review of this article, however, suggests that conceivably these could have been histamine headaches and that relief came from the extra amount of adrenalin excreted, as the result of the hypoglycemia, rather than through the antispasmodic activity of insulin as postulated by Tillum.

The author was not familiar with the term hypoglycemic migraine<sup>8</sup> when he started holding a headache clinic at the University Hospital, Ann Arbor, in 1947. He used the term migrainoid headache due to hypoglycemia to describe the first patient he saw in whom spontaneous hypoglycemia seemed to be the etiological factor in recurrent unilateral headaches. A summary of this case follows.

**Case Report.** CASE 1. I. P., a 30 year old, white male graduate student, stated that he had had "migraine headaches" for 15 years. These were preceded by an "aura". "The headache is located most often in the right or left temple area, accompanied by scotomata and nausea and vomiting and lasts from several hours to as long as 3 days. They come on 2 to 4 times a month." The patient was treated by 3 different physicians for "migraine headache". He had never had any relief from ergotamine tartrate.

The *Family History* was negative except that the father, paternal grandmother, and two brothers had "migraine headaches." The remainder of the history was negative.

\* Presented at a Regional Meeting of the American Federation for Clinical Research, March 4, 1949, Ann Arbor, Michigan.

*Physical Examination* disclosed a blood pressure of 140/90, pulse 80, temperature 98.6, respirations 20. Other than the slight elevation in blood pressure the examination was entirely normal.

When seen in the headache clinic the patient was loath to discuss his headaches and stated that if they could not be stopped he planned to drop out of school. After close questioning, the following additional information was obtained. His so-called "aura" consisted of a feeling of weakness, drowsiness and fatigue; this was followed by nervousness, tremor and wet palms. Sometimes he saw lights during this period. About 1 hour after the onset of drowsiness his headache would start and build up to a severe unilateral throbbing ache, usually in either the right or left temple. The patient had noticed that food prior to the onset of the nervousness might abort the headache.

Because of this suggestive story the patient was given a glucose tolerance test, following a 3-day preparation<sup>9</sup>, with the following values:

|                |         |    |    |    |    |    |    |    |
|----------------|---------|----|----|----|----|----|----|----|
| Hours          | Fasting | 1  | 2  | 2½ | 3  | 3½ | 4  | 5  |
| B1. sugar      |         |    |    |    |    |    |    |    |
| Mg. p. 100 cc. | 59      | 89 | 68 | 47 | 42 | 17 | 33 | 40 |

A headache came on between 3½ to 4 hours and lasted for about 12 hours.

The very low value of 3½ hours and the fasting value of 59 mg. suggested a neoplasm of the pancreas, so the patient was admitted to the hospital and placed on a provocative diet consisting of 50 gm. of protein, 50 gm. of carbohydrate and 1,200 calories per day, for 3 days. Fasting blood sugars during this time were 72 mg., 73 mg., and 60 mg. It was thought that this ruled out a tumor and that the patient had rather severe functional hyperinsulinism.

On several other occasions the patient had glucose tolerance tests but while they were low at the 3 to 4 hour period they never got below 40 mg. Each time, however, a headache was precipitated.

The patient was placed on a diet of 150 gm. of protein, 190 gm. of fat, and 75 gm. of carbohydrate. His headaches ceased with the exception of 2 attacks, and both followed breaks in the diet.

The patient was seen 14 months later and had had no other recurrence, and was reportedly free of the attacks 24 months after the diet was instituted.

Because of the dramatic results in this case following treatment of the spontaneous hypoglycemia, 5-hour glucose tolerance tests were done on patients with

headaches where there was the slightest possibility that spontaneous hypoglycemia existed. All patients were prepared for 3 days prior to the tests<sup>9</sup>.

Of 92 patients seen over a 17 months period, 11 had headaches of a migrainoid nature that seemed to be associated with spontaneous hyperinsulinism. Two of these were further complicated by having histamine headaches in addition. The data concerning these patients are shown in more detail in Table I.

**Discussion.** Cases M. G. and A. F. received almost complete relief on the high-protein, low-carbohydrate diet, but headaches continued to occur at infrequent intervals. These seemed typical of the histamine types described by Horton<sup>10</sup>, and responded to histamine desensitization. It was necessary to continue the diet, however, as headaches returned when the diet was discontinued. On the combined type of treatment, complete relief was obtained.

In the case of C. N., relief was obtained for 2 months, at which time the patient developed nausea (associated with pregnancy) and could not take the diet for almost a month. The headaches occurred 3 times during this period. With the cessation of the nausea and resumption of the diet the headaches were again controlled.

The two cases, V. J. and F. C., had hypoglycemic symptoms about the time that the low blood sugar was reached; neither had headaches associated with hypoglycemia or received benefit from the diet. This should emphasize that the headaches must be reproduced during the test before the diagnosis can be established.

It can be seen from Table I that only 3 patients gave a history commonly associated with hypoglycemia, namely, weakness, sweating, dizziness, and nervousness. In each case the patient volunteered the information

that an "aura" preceded the headache. Close questioning revealed that it was not a true "aura". Hypoglycemia was suspected in the other cases because the headaches usually started in mid-morning or mid-afternoon. In one case, E. N., they only occurred on Sunday morning and it was discovered that

he varied his usual breakfast of bacon and eggs to waffles and syrup on Sunday.

It is believed that the variation in time between the lowest blood sugar recorded and onset of the headache is due to the fact that the low point recorded may not represent the actual

TABLE I.--DATA CONCERNING 13 PATIENTS

| Patient | Age | Sex | History                      |      |                     |                    |                                 |                           |                        | 5 Hr. G. T. T.           |                                    |   |                              | Relief with diet | Follow-up      |
|---------|-----|-----|------------------------------|------|---------------------|--------------------|---------------------------------|---------------------------|------------------------|--------------------------|------------------------------------|---|------------------------------|------------------|----------------|
|         |     |     | Duration of symptoms (years) | Aura | Nausea and vomiting | Type of headache** | Interval between attacks (days) | Length of attacks (hours) | Previous relief with H | Lowest blood sugar mg. % | Time of lowest blood sugar (hours) | Interval between low blood sugar & headache (minutes) | Duration of headache (hours) |                  |                |
| IP      | 30  | M   | 15                           | Yes  | Yes                 | U                  | 7                               | 12:48                     | No                     | 17                       | 3½                                 | 30  | 12                           | Yes              | 2 Yrs.         |
| VJ      | 31  | F   | 6                            | No   | Yes                 | U                  | 28                              | 24:48                     | Occ.                   | 30                       | 3½                                 | No Headache   |                              |                  |                |
| FC      | 27  | M   | 20                           | No   | Yes                 | B                  | 2:30                            | 12                        | Occ.                   | 53                       | 4                                  | No Headache   |                              |                  |                |
| MI      | 23  | F   | 10                           | Yes  | Nausea              | U                  | 30                              | 12:36                     | No                     | 41                       | 3                                  | 45  | 18                           | NC               | 18 Mos.        |
| FR      | 21  | F   | 14                           | Yes  | Yes                 | U                  | 7:14                            | 4:6                       | No                     | 46                       | 3                                  | 60  | 3                            | ?                | Did Not Return |
| EN      | 36  | M   | ½                            | No   | Yes                 | U                  | 7                               | 12:15                     | No                     | 42                       | 3                                  | 15  | 12                           | Yes              | 12 Mos.        |
| MC      | 25  | F   | 1                            | No   | Yes                 | B                  | 2:7                             | 12:15                     | No                     | 38                       | 3½                                 | 0   | 6                            | ?                | Did Not Return |
| AA      | 45  | F   | 35                           | No   | Nausea              | B                  | 21:28                           | 24:72                     | Partial                | 39                       | 4½                                 | 120   | 12                           | Yes              | 4 Mos.         |
| MG      | 41  | F   | 23                           | Yes  | Yes                 | U                  | 7                               | 24:36                     | Occ.                   | 36                       | 3½                                 | 0   | 6                            | Partial          | 6 Mos.         |
| CN      | 27  | F   | 1                            | Yes  | Yes                 | U                  | 7:14                            | 12:48                     | No                     | 31                       | 3                                  | 15  | 3                            | Almost Complete  | 4 Mos.         |
| AF      | 40  | F   | 4                            | Yes  | Yes                 | U                  | 14                              | 12:72                     | No                     | 32                       | 3                                  | 30  | 4                            | Partial          | 6 Mos.         |
| FC      | 26  | M   | 6                            | No   | Yes                 | U                  | 21                              | 12:15                     | No                     | 29                       | 3½                                 | 0   | 12                           | Yes              | 14 Mos.        |
| CC      | 30  | F   | 3                            | Yes  | Yes                 | U                  | 7                               | 24                        | No                     | 37                       | 3½                                 | 30  | 6                            | Yes              | 4 Mos.         |

\* Aura was compatible with symptoms of hypoglycemia

\*\* U Unilateral

B Bilateral

lowest blood sugar, but might have either followed or preceded it.

Because of the relatively high incidence of this condition in a series of 92 patients suspected of having migraine headaches it is felt that this syndrome should be stressed to the profession. If care is used, a number of patients suffering with migraine may be correctly classified and treated.

When the term migraine was originally used, it served a definite and useful purpose in describing a syndrome. Many types of headaches which formerly would have been diagnosed as migraine are now known by a more descriptive name, such as histamine headache<sup>10</sup>, Williams headache<sup>16</sup>, and others. It is within the realm of possi-

bility that eventually the term migraine will no longer be needed, as the etiology for the several syndromes that are grouped under this term will be known. Because of this it is suggested that the term migraine be abandoned in the syndrome described, and that hypoglycemic encephalalgia or hypoglycemic headache be used.

Summary. 1. Eleven cases of recurring migrainoid headaches associated with functional hyperinsulism are reported. 2. Improvement or complete relief followed therapy with high-protein diet. 3. The term hypoglycemic encephalalgia or hypoglycemic headache is suggested as being most descriptive of this syndrome.

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# PROGRESS OF MEDICAL SCIENCE

## SURGERY

UNDER THE CHARGE OF

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## PERICARDIAL AND CARDIAC SURGERY\*

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THE recent work of Blakemore and Lord<sup>15</sup>, Gross<sup>17</sup>, Crafoord<sup>30</sup>, and Blalock and Taussig<sup>20</sup> has given impetus both to experimental vascular surgery and to its clinical application. At present, the most vital of all vascular structures, the heart, is receiving the direct surgical attack that Allen and Graham<sup>2</sup>, Cutler<sup>31</sup>, and Beck<sup>9</sup> advocated and pioneered. The amazing ingenuity of Beck<sup>10</sup>, Blalock and Hanlon<sup>18</sup>, Murray<sup>66</sup>, and Jongbloed<sup>60</sup> portends the alleviation of many heart ailments heretofore considered not amenable to surgical or medical treatment. The surgery for relief of the complications of patent ductus arteriosus, coarctation of the aorta and the tetralogy of Fallot is in reality surgery of the great vessels, although pulmonic stenosis has received some attention from the cardiac ap-

proach. It is, therefore, the intention of the writer to review recent developments of surgery of the pericardium and heart. Topics to be considered include:

I. TRAUMA. *a*, Contusions. *b*, Penetrating wounds. *c*, Foreign bodies.

II. TUMORS.

III. PERICARDITIS. *a*, Acute. *b*, Chronic.

IV. MYOCARDIAL ISCHEMIA.

V. VALVULOPLASTY.

VI. SEPTAL DEFECTS.

VII. MISCELLANEOUS ADJUNCTS. *a*, Anesthesia. *b*, Resuscitation. *c*, Cardiac catheterization. *d*, Mechanical heart.

TRAUMA. Contusions of the heart result from direct blows over the precordium. The most frequent causes are falls and trauma from steering wheels of automobiles. Patients who complain of chest pain following such accidents

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should be examined and have an electrocardiogram and chest plate taken. If no early findings are noted but discomfort persists, or if the initial tracing reveals myocardial damage, further tracings should be taken. This routine will occasionally demonstrate early development of an aneurysm of the ventricle. Such aneurysm may be benefited by surgery, using either fascia lata<sup>4</sup> or 1.5 mil du Pont Polythene, type NV-7-14<sup>74</sup>. Poppe and de Oliveira<sup>74</sup> have reported the use of cellophane wrapping for syphilitic aneurysms and we have used the previously mentioned polythene at the Dearborn Veterans Hospital in 1 fusiform abdominal aortic aneurysm and in 1 saccular aneurysm of the aortic arch. All symptoms were relieved in the first case; the second is too recent to evaluate. In using this material over a ventricle, the edge of the polythene is sutured to the myocardium at the base of the aneurysm and the subsequent reaction results in shrinking of the lesion by fibrosis from without.

Penetrating wounds of the heart result usually from stab or gunshot injury. It was the successful suture of a stab wound of the heart by Rehn<sup>76</sup> in 1896 that proved the heart would tolerate surgical interference. Prior to that time anyone suggesting surgery of the human heart was looked upon with disfavor. At present it would seem that the mortality from penetrating heart wounds in patients arriving alive at a well-equipped hospital should not be excessive. The report of Bigger<sup>14</sup> in 1939, including cases from members of the American Association for Thoracic Surgery, American Surgical Association, and Southern Surgical Association, revealed a 50% mortality in 141 cases. Blau<sup>21</sup> reported a 22.2% mortality in 27 cases. Samson<sup>79</sup> recently reported on 75 patients with wounds of the heart and pericardium resulting in 40% mortality. This latter group, however, concerned

war wounds and 18 of the 75 patients had wounds elsewhere in addition to the thoracic cage.

The surgical treatment of penetrating heart wounds is imperative in cases persistently bleeding and having a pericardiopleural communication. An occasional case with cardiac tamponade may be treated with aspiration and observation but even such a case occasionally bleeds several days after the injury. In general, therefore, it is wise to explore the case of tamponade as well as in case of persistent bleeding. General anesthesia with tracheal intubation has been most satisfactory. Surgical approach through the left parasternal route will be adequate in most cases. If the pleura is intact it may be pushed off the pericardium. The transpleural route, however, is faster and if speed is essential one should not hesitate to open the pleura. The pericardium is widely opened and an apical suture inserted if traction is desired. Silk or cotton is used to close the heart wound. The pericardium is partially closed, allowing drainage either into the pleural space or into the space beneath the incisional flap. Aspiration of either of these spaces will remove the postoperative fluid as required.

Knowledge of the handling of foreign bodies in or in close relation to the heart has been increased by the recent reports of Harken<sup>49,51,52</sup>. Indications for removal of intracardiac foreign bodies are clearly defined<sup>52</sup>. These include: 1, To prevent embolus of the foreign body or the associated thrombus; 2, to reduce the incidence of bacterial endocarditis; 3, to avoid recurrent pericardial effusions; 4, to diminish the danger of myocardial damage with subsequent rupture or myocardial aneurysm.

Most foreign bodies of the heart result from penetrating wounds. Rarely a missile is carried by embolism. Of interest too, is the movement of a mis-

sile in the heart itself. Harken operated upon one patient 3 times because of movement of the missile from one chamber to another during operative manipulation. Of 56 foreign bodies in, or in relation to the heart, 13 were removed from the chambers of the heart. There were no deaths in this series in contrast to 8 deaths in 47 operations in the collected cases reported by Decker<sup>37</sup>. The methods of localization, operative approaches and technic of removal are clearly presented by Harken<sup>40</sup>.

**TUMORS.** Primary tumors of the heart are much less frequent than metastatic ones. The most frequent primary tumors in order named are myxomata, sarcoma, rhabdomyoma and fibroma. The rarity of ante mortem diagnosis of intracardiac tumor is emphasized in the report by Mahaim<sup>61</sup>. This author found only 3 established primary intracardiac tumors recognized before death. Many of these tumors, particularly the myxomas, are polypoid and intra-auricular. They would, therefore, be accessible to the surgeon which fact calls for a greater effort toward early diagnosis of this lesion. Findings suggestive or diagnostic of a tumor of the heart include unexplained and intractable cardiac failure, unexplained changes in cardiac rhythm, sounds, and size as judged by physical, Roentgen and electrocardiographic examinations, and development of a hemorrhagic pericardial effusion.

**PERICARDITIS.** Acute suppurative pericarditis has become less frequent with the advent of penicillin and the sulfa drugs. Since the disease is secondary to a streptococcal, staphylococcal or pneumococcal pneumonia in most instances, adequate treatment of the primary condition usually prevents the pericardial involvement. Although instances of recovery following aspiration and penicillin instillation have been reported<sup>3,92,93</sup>, the danger of tamponade is always present and this complication

calls for close observation. If aspiration does not give immediate and adequate relief, surgical drainage should be performed. Brock<sup>22</sup> states that the gravity of the patient's condition should not be allowed to decide against operation but rather in favor of it. Carter<sup>26</sup> mentions the impossibility of removing by aspiration performed anteriorly the pus which uniformly collects behind the heart. He states the most effective treatment is early surgical drainage supplemented by intensive systemic and local penicillin therapy. The surgical drainage is easily accomplished by a left parasternal incision. The pericardium is widely opened and sutured to the skin. Intrapericardial irrigation is then performed as needed.

The etiology of chronic constrictive pericarditis is generally thought to be tuberculosis. Blalock and Levy<sup>19</sup> found positive evidence of tuberculosis in 24 of 42 patients with pericarditis. Paul, Castleman and White<sup>73</sup> proved tuberculous involvement in only 9 of 53 patients. Many of the patients with this disease are in such serious condition that pericardiectomy must be delayed. Conversely the longer the heart labors under the strain of its fibrous or calcific coating, the more atrophy will be present in the myocardium. It is probably this long disuse atrophy that causes the permanent damage which will not allow a cure in some cases. At the present time it is hoped that streptomycin therapy will allow an earlier surgical approach which should give improved results. Since Hallopeau<sup>48</sup> first performed pericardiectomy in 1910, authors of large series have shown the steadily decreasing operative mortality. In 1939, Heuer and Stewart<sup>56</sup> collected 143 cases with 34% cures and 17.5% improved. The operative mortality was 32.8%. Harrington<sup>53</sup> reported a 25% mortality in 24 cases and in discussion of Harrington's paper, Beck<sup>8</sup> reported a series of 46 patients with 19.6% oper-



ative mortality; 71% were cured or improved. A more recent report by Heuer and Stewart<sup>57</sup> cites 18 cases with no deaths and 83% cured or improved. The operative technique has been well described by Churchill<sup>27</sup>, Heuer and Stewart<sup>57</sup>, Harrington<sup>53</sup>, Blalock and Burwell<sup>71</sup> and needs no amplifying.

**MYOCARDIAL ISCHEMIA.** The surgery for alleviation of angina pectoris and coronary atherosclerosis is the most challenging of cardiac problems. The great number of deaths from this disease every year attest to its importance. From a more selfish viewpoint, physicians are at or near the top in group incidence of coronary disease. H. L. Smith<sup>81</sup>, in a review of the case records of 307 doctors, 300 bankers, 304 lawyers, 306 clergymen, 306 laborers, and 308 farmers of about the same age, found 33 instances of coronary sclerosis in physicians with only 16 in bankers the next highest group. Certainly these figures are subject to statistical error, but the difference in the rate of incidence is so striking that it appears significant.

The surgical approach to the treatment of angina pectoris and myocardial ischemia has included sympathectomy, total thyroidectomy and revascularization procedures. Sympathectomy has been advocated and performed to varying extents since Jonnesco<sup>61</sup> first performed the operation. Although various writers have stressed necessity of excision of different segments of the cervico-thoracic chain, unilaterally or bilaterally, Heinbecker's<sup>74</sup> work indicates the superiority of excision of the inferior cervical sympathetic ganglia: the first, second and third thoracic ganglia which suffices to interrupt the pain pathways. White<sup>90</sup> advocates paravertebral alcohol injection of dorsal sympathetic ganglia and this procedure has given very good results in the hands of those performing the procedure frequently. The occasional associated

neuritis may be, however, a very annoying sequel. Total thyroidectomy, while lowering the metabolic activity of the body, has the disadvantage of producing hypothyroidism with its disturbing symptoms. The chief argument against both sympathectomy and thyroidectomy is that the fundamental problem, poor blood supply to a local area, is not relieved. In coronary sclerosis we are fortunate in that at first the larger arteries are narrowed and later the smaller vessels. Thus there is ample opportunity to develop a collateral blood supply after the disease has started.

Since 1932 Beck<sup>7, 60, 84</sup> has pioneered in revascularization experiments and their clinical application. Early experiments made use of grafts of pectoral muscle, pericardium and mediastinal fat to abraded myocardium. Later, powdered asbestos was placed on the abraded surface to create an inflammatory reaction in which collateral supply developed. By suturing the pericardium or mediastinal fat to this abraded area, an adhesive pericarditis was created through which a new vascular supply was available to the myocardium. Feil<sup>44</sup>, in 1943, appraised the results of Beck's operation in 37 patients since the first patient was operated upon in 1935. Of 23 patients surviving the operation, 14 were still living with 9 in excellent condition and 5 in good condition.

O'Shaughnessy<sup>70</sup> reported his first experimental work on this subject in 1936. He demonstrated the presence of a collateral circulation by dye injection through the vessels of tissue grafted to the myocardium. In several subsequent reports, O'Shaughnessy and associates<sup>77, 76, 71, 72</sup>, reported their results with cardiomentopexy and cardiopneumopexy. The final report<sup>76</sup> recorded 20 patients operated upon with 12 still living. Most of these were improved and the majority were back at work. Others who did similar work include

Lezius<sup>63</sup>, who accomplished cardiopneumopexy experimentally, and Carter<sup>26</sup>, who reported 2 cases of cardiopneumopexy, one decidedly improved and the other dying of massive infection in 36 hours.

Heinbecker and Barton<sup>55</sup> have mentioned the danger of producing ventricular fibrillation in the human during suture of a graft to the myocardium. Experimentally in dogs they used ½% to 5% sodium morrhuate injected in the pericardial sac, adding 0.4 gm. powdered aleuronat. The pericardium was then sutured to retrosternal tissues. In periods varying from 3 weeks to 6 months the dogs were autopsied and new collateral blood supply was demonstrated.

Thompson and Raisbeck<sup>67</sup> used talc powder to induce an adhesive pericarditis and Thompson<sup>66</sup> reported the results of this operation upon 38 patients. More than 70% had good to excellent results. Four patients were classed as poor results after showing less than 33% improvement postoperatively.

In 1946 Fauteux<sup>40</sup> published experimental work on dogs in which the internal mammary artery was anastomosed with the coronary sinus. This procedure prevented the ventricular fibrillation so frequent following ligation of the left circumflex coronary artery. The same author<sup>41,42</sup> reported experimental and clinical work on coronary disease in which he ligated the great coronary vein and resected the nerve pathways at the root of the aorta and the origin of the coronary arteries. Sixteen patients were operated upon with 3 operative deaths. Eleven patients were alive with objective improvement 3 months to 6½ years after surgery.

Vineberg and Jewett<sup>80</sup> recently reported experimental work in implantation of the left internal mammary artery into the muscle of the left ventricle. In 9 of 10 animals the artery

revascularized the surrounding structures and in 2 instances there was anastomosis directly with the left coronary artery.

In 1943, Roberts, Browne and Roberts<sup>78</sup> accomplished a unique procedure in animals by connecting the coronary sinus to the brachiocephalic, subclavian or innominate artery via a glass cannula. Subsequent examination of the myocardium revealed a complete injection of the capillary network after dye was injected into the coronary sinus.

In May, 1948, Beck and associates<sup>13</sup> reported their newest attack on the treatment of angina pectoris and myocardial ischemia. The objective of the new procedure is to improve the oxygen supply to the myocardium by a shunt of arterial blood back through the coronary sinus and coronary veins. In the dog the coronary sinus is a very thin-walled structure and presents technical difficulties in performing a blood vessel anastomosis. To overcome this difficulty Beck utilized a 2 stage operation, tying off the coronary sinus at the first operation and 10 days later anastomosing a segment of carotid artery from the aorta to the coronary sinus. The 10 day wait was sufficient for the ligated sinus to thicken enough to allow easier suturing. In 50 normal dogs there was 70% mortality following ligation of the left descending coronary artery. In 10 dogs with patent grafts from the aorta to the coronary sinus, 8 survived, one dying 8 days after operation, the other dying in 13 days. In this latter group there was no evidence of extensive myocardial damage, whereas the control group showed considerable myocardial injury. In the Wayne University Surgical Research Laboratory, Dr. Prescott Jordan and I have performed Dr. Beck's 2 stage operation upon 60 dogs. The external jugular vein was utilized for the free graft. Technical difficulties were gradually overcome at the expense of a high mortality. The

last 15 dogs however, have survived the procedure and appear to be in good health. After 2 years of experimental work Beck operated upon the first patient, January 27, 1948. In the human the procedure can be done in one-stage, since the coronary sinus is larger and consequently easier to handle. In the first patient a segment of brachial artery was used for the graft and the operative procedure was completed but death occurred in the immediate post-operative period. In February of 1949, Beck<sup>11</sup> reported 2 similar procedures and presented the patients in their early postoperative period during the 6th Annual Assembly of the Central Surgical Association. In these latter 2 cases a vein was utilized for the graft.

In order that the proper patients be chosen for such an operation it should be remembered that medical means will alleviate the symptoms in all but 10 to 20% of persons having angina pectoris and coronary sclerosis. Also it should be realized that at present some of the above-mentioned procedures are technically difficult and with poor risk patients the mortality will be high. In revascularization, however, there is a ray of hope that with added experience the operative risk will be reduced. It is our opinion that the principle which Dr. Beck has demonstrated of the utilization of a vein to carry arterial blood to an ischemic area is an important one. Johnston and Jordan<sup>50</sup> have successfully utilized this principle in treating obliterative arterial disease in patients and have tested its efficacy in laboratory animals.

**VALVULOPLASTY.** Experimental cardiac valvular surgery has made considerable progress since the end of World War II. Earlier in the century the foundation for this work was laid by Sir Lauder Brunton's<sup>51</sup> suggestion that surgery might relieve the symptoms of mitral stenosis. Much controversy was created by this suggestion, the opponents claim-

ing any incision in the stenotic mitral funnel would only create mitral insufficiency. After much laboratory research, Cutler<sup>33</sup> in 1923 performed the first operation in the human for relief of mitral stenosis. In this instance a valvulotome was inserted through the ventricular wall and incision of the valve performed blindly. This patient lived 4½ years and was believed to have been improved. Two more patients were operated upon with the valvulotome before Cutler, Levine and Beck<sup>34</sup> first used their cardiovalvulotome, an instrument somewhat similar to one previously invented by Allen and Graham<sup>1</sup>. This was used in 7 patients but only the first survived. These cases were summarized by Cutler and Beck<sup>32</sup> in 1929.

A very ingenious method for heart valve reconstruction was worked out by Murray, Wilkinson and MacKenzie<sup>60</sup> in 1938. This group desired to replace one of the diseased mitral cusps with a new cusp fashioned from a vein. They used a cardiovalvulotome and approached the lateral cusp of the mitral valve through the left auricular appendage. The lateral cusp was resected and the instrument withdrawn. A segment of external jugular vein was then inverted and drawn into a cannula which was inserted through the wall of the left ventricle in the position of the resected cusp. The cannula was then withdrawn, leaving the vein in the position of the cusp and allowing the vein to be anchored by sutures to both sides of the left ventricle. At the time of the report, 2 animals so treated were living and well.

An approach to the treatment of aortic stenosis was reported by Smithy and associates<sup>62,63</sup>. For the relief of this lesion a valvulotome was utilized and the approach was through the aorta. Bleeding was so troublesome that an approach through the ventricle was subsequently attempted and this was

found to be safer and simpler. The authors, however, recognized the 2 difficulties with simple incision of the stenotic valve, namely, creation of aortic insufficiency early, and later, following fibrosis and repair, re-establishment of the aortic stenosis.

Campbell<sup>25</sup> reported the use of an artificial aortic valve made of a plastic, methyl methacrylate. Another approach and perhaps the most practical to date, is that of Templeton and Gibbon<sup>85</sup> in reconstruction of a tricuspid valve. Under direct vision these workers removed a valve cusp and reconstructed a new valve with either pericardium or vein. In this procedure both vena cavae and the azygos veins were clamped and the right auricle then opened. It was found that the dog withstood clamping of the vena cavae and azygos return for 9 minutes without serious result. During this 9 minute period the valve cusp was carefully removed. The auricular incision was then closed and a new valve of pericardium or vein cut to replace the piece removed. Fine silk sutures were then placed in the valve with the needle remaining on each suture. Clamps were again placed on the veins and the auricular incision reopened. The new valve was quickly sutured into position and the auricle again closed. Of 19 dogs so treated, 7 were living and well 3 weeks after operation. Five survived 7 to 11 months after operation. Morphologically and clinically the pericardial valves gave results superior to the vein grafts.

The direct attack on pulmonary stenosis has recently been advocated by Brock<sup>22</sup>. He states, however, that the operation he proposes would relieve valvular stenosis but not subvalvular stenosis, which Blalock<sup>16</sup> emphasizes is the usual defect in the tetralogy of Fallot. His experience, too is in keeping with that of several previous workers who attempted to use the cardiovalvulotome but usually had

to resort to the blind approach with the tenotome alone. Three patients were subjected to the procedure of incising the stenotic orifice and then widening the opening with forceps. The first patient developed a saddle embolus postoperatively but recovered. The second made an uneventful recovery and the third developed a hemiplegia that is slowly improving. All the patients have shown improvement from the stenosis but the follow-up is of short duration.

It is interesting to note that most of the early investigators considered the pathological in contrast to the pathophysiological approach which Harken<sup>50</sup> and associates have recently brought forth. The early concept was that stenosis of a valve was present and, therefore, in some manner that valve should have a large opening. Harken's study offers criteria for selection of patients and the operation best suited for each group. Patients selected for operation should have cardiac symptoms of mitral stenosis unrelieved by any medical therapy. They should also have a minimum of involvement of other valves and no active rheumatic disease. A classification of patients into 3 groups based on their physiological state has been made. Group A includes patients with a low resting cardiac output, which is unchanged or even decreased on exercise, and with an elevated pulmonary artery pressure. Mitral obstruction is paramount in this group and valvuloplasty should be helpful. Group B differs in that the resting cardiac output is within normal limits and usually increases with exercise. Here mitral regurgitation may be more important than stenosis. If the left auricular pressure is high, as measured by cardiac catheterization, an artificial interatrial septal defect may be beneficial. Group C includes patients whose symptoms of pulmonary edema and rapid heart action are not controlled by medical

treatment. Harken advises 2-stage bilateral resection of the inferior cervical ganglion and the first 4 or 5 dorsal sympathetic ganglia. He states that the relief afforded is through the production of a slower heart rate or through the interruption of pain fibers.

Five operations have been performed for patients in these various groups: 2 valvuloplasties, 2 artificial interatrial septal defects and 1 denervation. One death occurred 24 hours after a valvuloplasty. The objective attitude of this report is so noteworthy that it would seem to be a yardstick which might be used to evaluate future surgery of valvular disease.

**SEPTAL DEFECTS.** As mentioned by Harken and associates<sup>50</sup>, production of an artificial septal defect would benefit certain types of heart disease. Most pronounced would be the need of an interatrial septal defect for high left auricular pressure and pulmonary venous hypertension. Conversely, closure of a congenital septal defect may change a cardiac cripple into a normal person. Ingenious methods of producing septal defects have been described by Cohn<sup>28</sup>, and by Blalock and Hanlon<sup>18</sup>. The latter have resected about 2 cm. of interatrial septum under direct vision in 31 dogs. Exposure is obtained from the right side and a special curved clamp used on the right auricle. Bleeding from the pulmonary vein is controlled by traction sutures and the vein and auricle are opened under direct vision. Three dogs died 1 to 9 days after surgery and others were autopsied at varying intervals. Five were still alive and well 4 to 7 months after the operation.

The most spectacular work in repair of septal defects has been reported by Murray<sup>67</sup>. On the basis of excellent anatomical knowledge he has passed a needle across the septal defect and then pulled fascia lata, silk or cotton after. A combination of factors comes

into play in closing the defect. The suture substance, especially fascia, is of much importance but the narrowing of the anterior-posterior diameter of the heart when the suture is snugged up is also important. A third adjunct is the thrombosis around the suture material. When it is thought that sufficient thrombosis has taken place, heparin is started and further thrombosis thus avoided. Murray<sup>68</sup> reported on 14 septal repairs, 5 interauricular and 9 interventricular: 1 interauricular case died, 2 had good results and 2 were improved; 5 interventricular patients survived. In general the results have been very encouraging and certainly deserve further clinical trial.

**MISCELLANEOUS ADJUNCTS.** The anesthesiologist can carry on artificial pulmonary ventilation quite satisfactorily. However, artificial circulation is but in the experimental phase notwithstanding the operator's ability to massage the heart for a limited time. In the efforts to protect the heart against severe circulatory depression, against reflex depression and cardiac arrest, anesthesia becomes particularly important. Any prophylaxis that can be effective is certainly more valuable than elaborate plans for cardiac resuscitation. The basic principles that should be followed are: 1, maintenance of adequate and complete oxygenation; 2, use of drugs that depress the vagal activity and particularly do not stimulate this activity; 3, constant and careful observation of the circulation by following the pulse and blood pressure plus direct observation of cardiac activity during the surgery.

If manipulation is shown to produce marked cardiac slowing or irregularity, steps should be taken to depress these reflexes. It has been found that certain anesthetic drugs are effective in depressing both parts of the autonomic nervous system. Ether is a good example. This drug causes depression of

vagal activity and is very safe for cardiac surgery when properly administered. On the other hand, cyclopropane has been found to increase the sensitivity of cardiac autonomic mechanisms to drugs such as epinephrine while the vagal activity is not depressed in many patients. If cyclopropane is to be employed during cardiac surgery, some drug must be administered to depress the vagal reflexes. This can be done satisfactorily with intravenous procaine given continuously in 1% concentration. However, the safety of this plan is probably not equal to that of using ether. In the administration of any anesthetic drug to patients with lowered cardiac reserve, the skill and experience of the anesthetist is highly important. Experience has shown that drugs administered slowly have an added safety factor since one may check changes in circulation rapidly enough to stop use of the drug. All too often circulatory changes go unnoticed and deaths are described as being sudden. This is sometimes because of failure to observe changes that have occurred at some previous time. Sudden cardiac deaths are either due to reflex activity, sudden overdose of the anesthetic drug or sudden drops in blood pressure, particularly in patients who have been accustomed to hypertension. All these conditions become much more important in circulatory and cardiac surgery where severe hemorrhage may occasionally occur.

Occasionally the catastrophe of ventricular fibrillation or cardiac standstill will occur even with good anesthesia. If this happens, a method of resuscitation should be in the armamentarium of anyone doing cardiac surgery. Resuscitation has been studied by many workers. Markowitz and Mann<sup>65</sup> demonstrated the necessity of suitable intracoronary pressure in resuscitation of both a rabbit and a dog heart. After bleeding the organ completely and

removing it from the chest Ringer-Locke's solution was forced into the coronary vessels and the heart beat resumed. A solution containing epinephrine 1 to 50,000 was similarly used and the dog heart resumed beating. A similar resuscitation experiment with human hearts was reported by Kountz<sup>62</sup>. He studied 127 hearts obtained 5 minutes to 6 hours after death. Sixty-five of the hearts revived to ventricular contraction and 48 of the 65 developed regular cardiac mechanism for at least 2 hours. Hooker<sup>58</sup> induced ventricular fibrillation in dogs by electric shock. He then injected into the carotid artery a solution containing KCL 0.5%, NaCl 0.9% and heparin 0.25 mgm. per cc. in the amount of 13 cc. per kg. of body weight. This solution caused inhibition of the heart. After one minute a solution of  $\text{CaCl}_2$  0.023%, NaCl 0.9% in the amount of 25 cc. per kg. was injected. This solution by washing the excess of potassium out of the coronary bed and substituting a relative excess of  $\text{CaCl}_2$ , stimulated a normal cardiac rhythm. Wiggers<sup>91</sup> observed the change from ventricular fibrillation to normal rhythm following passage of a 60 cycle A.C. current with minimal strength of 1 amp. This change, however, would only occur when coronary occlusion was not present and if fibrillation had not been present more than 2 to 3 minutes.

Resuscitation of the human heart has been reported many times following cardiac standstill but very rarely after ventricular fibrillation. Dripps, *et al.*<sup>38</sup> described the successful revival of 4 patients in whom cardiac standstill had occurred. In 2 cases the delay of 5 to 8 minutes before the heart was manually compressed caused irreversible brain damage from which the patients expired  $2\frac{1}{2}$  and 4 days postoperatively. The other two patients survived and were mentally normal at the time of the report. Other cases of successful resus-

citation following cardiac standstill have been reported by Adams and Hand<sup>1</sup>, and by Touroff and Adelman<sup>88</sup>. In 1941 Beck<sup>7</sup> reported defibrillation in 2 patients but both died with 4 hours after restoration of normal rhythm. Beck, Pritchard, and Feil<sup>12</sup> described the only successful case of complete recovery from ventricular fibrillation in December, 1947. The technique used by this group includes use of a mechanical respirator, vigorous and regular cardiac massage, injection of 5 cc. of 2% procaine into the right auricle or ventricle, and momentary impression of an alternating current of 110 volts with 1.5 amp. through the heart.

Further experimental observations have been presented by Fauteux<sup>43</sup>. Effectiveness of electric shock was confirmed. Members of the cocaine group were found to be of value in reducing cardiac hyperirritability. Intra-auricular injection of 1 to 2 cc. of 0.5% barium chloride was found to be of value in increasing cardiac tone and the giving of blood intra-auricularly aided in prevention of circulatory failure.

New and improved aids for diagnosis of uncommon cardiac disorders are now being utilized to substantiate or refute clinical impressions. Angiocardiography as described by Robb and Steinberg<sup>77</sup> is now performed in many hospitals. Catheterization of the heart, introduced by Forssman<sup>45</sup> of Germany in 1929, and practiced first in this country by Courmand and Ranges<sup>29</sup>, has allowed pressure measurements and chemical studies from the various heart chambers. Its usefulness in the diagnosis of various cardiac malformations has been reported by Burchell and associates<sup>24</sup> who based their findings on 60 catheterizations. A later report<sup>46</sup> from the same clinic describes application of an oximeter for determination of the oxygen

saturation of whole blood during cardiac catheterization. Radiocardiography is the latest adjunct for the diagnosis of cardiac disorders. This consists of the graphic recording of the passage of radioactive blood through the cardiac chambers by means of a specially constructed ink-writing Geiger-Mueller counter. Prinzmetal and associates<sup>75</sup> have reported the first clinical studies with radioactive sodium.

Technical difficulties inherent in the handling of a sensitive beating organ such as the heart have undoubtedly delayed the progress of cardiac surgery. The possibility of oxygenating the blood mechanically was approached by Gibbon<sup>45a</sup> in 1939. Animal experiments demonstrated that the pulmonary artery could be safely occluded for from 10 to 25 minutes with the circulation being maintained by the oxygenator. An improved device capable of introducing as much as 30 cc. of oxygen per minute with rates of blood flow of 100 cc. to 500 cc. per minute was described by this same investigator<sup>45b</sup> 2 years later. Jongbloed<sup>60</sup> has recently announced the development of an apparatus which allows him to operate upon the hearts of dogs for an hour with the artificial system handling the pumping and oxygenating of the blood. The heart and lungs both have returned to normal status after this hour of non-function. With this experimental work for a basis, Jongbloed has constructed an artificial heart-lung system for use in the human. This system functions semi-automatically and has a capacity of more than 10 liters per minute. If such an apparatus proves feasible the direct surgical approach to cardiac tumors, valvular disease, septal defects and removal of mural thrombi is much closer than most of the medical profession would believe.

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# OPHTHALMOLOGY

UNDER THE CHARGE OF  
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## THE OCULAR FUNDI IN RELATION TO OPERATIONS FOR HYPERTENSIVE CARDIOVASCULAR DISEASE

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OPHTHALMOSCOPIC evaluation of hypertensive cardiovascular disease has taken on increasing significance since the advent of surgical therapy. The proper interpretation of lesions in the ocular fundi may be of considerable aid in the selection and rejection of candidates for sympathectomy. The observation of the effect of the operation on the retinal lesions themselves is of great interest. It is perhaps especially important to study the significance of recession of the retinal lesions with regard to the future prognosis of the patient.

The types of surgical treatment of the sympathetic nervous system used in an attempt to benefit patients who have high blood pressure have been many and varied. The first such operation was performed by Rowntree and Adson<sup>47</sup> in December, 1924, at which time they carried out a bilateral lumbar sympathetic neurectomy on a patient who had malignant hypertension. Brüning<sup>7</sup> had previously suggested sympathectomy for this disease, but had not operated on any patients. Following this initial impetus there

has been a progressive evolution in the types of procedure carried out. All these operations are directed toward a denervation of the splanchnic bed. At present, the majority of surgeons do a bilateral resection of the greater, lesser and least splanchnic nerves, a partial celiac ganglionectomy, and extirpation of the sympathetic ganglia and trunks from the fourth or fifth thoracic segment down to the second or third lumbar segment. Some surgeons do even more extensive sympathectomy, but others believe that less resection is sufficient in some patients. There are, of course, many variations in opinions and in techniques, too numerous to detail here.

There is still controversy as to the relative value of surgical and medical treatment of hypertension, in the alleviation of symptoms, lowering of the blood pressure and prolongation of life. The methods of estimating the efficacy of treatment are extremely varied, so much so that it is difficult to assess and to compare the results obtained by the various investigators. In a disease of unknown origin, diverse

manifestations and lack of clear-cut demarcation into clinical groups, a great deal of justified controversy is inevitable.

Many attempts have been made to classify patients with hypertensive cardiovascular disease<sup>8,13,19</sup>. None of these classifications has been accepted by all investigators, chiefly because none seems to answer all questions perfectly. However, the Keith-Wagener-Barker classification<sup>31</sup>, in which hypertensive patients are separated into 4 numbered groups on the basis of retinal and associated general signs, has seemed to lend itself to the most accurate delineation for treatment and for prognostic purposes. Most of the reports on the results of sympathectomy in the literature have used this classification or a modification of it. However, because of differences in interpretation of this grouping or because of attempts to change or extend the classification, very few reports are readily comparable. In addition to the clinical grouping of the disease, one of us (H.P.W.) has for many years used and taught the meticulous grading of the retinal arteriolar changes (sclerosis, narrowing and spasm) on the basis of 1 to 4, as portrayed in the publication by Wagener, Clay and Gipner<sup>60</sup>.

The average prognosis in various types or grades of hypertensive cardiovascular disease under a purely medical regimen has been well worked out by several groups of investigators, notably Wagener and Keith<sup>59</sup>, Brana and Radnai<sup>6</sup>, and Palmer, Loofbourov and Doering<sup>35</sup>. However, the course in an individual patient is very difficult to predict. Therefore, an adequate evaluation of the effect of surgical treatment on the course of hypertensive disease requires postoperative observation for several years of a considerable number of patients in each of the various groups. It was well stated by Evans and Bartels<sup>12</sup> that to

ascertain the results of sympathectomy at all we must "wait 20 years in Group II cases, and 10 years in Group III cases to demonstrate that this procedure will check cardiovascular degenerative disease." Data on some rather large groups of patients observed for a considerable period have been reported recently. Additional studies should become available within the next decade.

Most reports deal with the effects of sympathectomy both on the hypertensive disease and on the local lesions in the retina. However, some authors stress the determination in the retina of criteria for the selection and rejection of patients for sympathectomy. Bedell<sup>5</sup>, for instance, stated that "the ophthalmologist should be able to state with reasonable certainty whether a given fundus pattern indicates a favorable outcome, one of doubtful value, or a disappointing result" and that "the ophthalmologist must advise for or against surgical intervention." Bedell stated that, if fulminating retinopathy or papilledema were present, there was little likelihood of prolonged benefit from operation. In his opinion operation is contraindicated in the presence of definite arteriosclerosis, round, deep, red granular hemorrhages, recent closure of a retinal artery or sudden occlusion of the central vein. In his discussion of Bedell's paper, Gibson<sup>19</sup> emphasized that patients with considerable chronic retinal arteriolosclerosis receive by and large the least benefit from surgical treatment, while those with considerable vasospasm but little sclerosis receive the most benefit.

Gans<sup>17</sup> thoroughly studied 15 patients before and after the subtotal to total sympathectomy of Grimson<sup>22</sup>, devising a rather ingenious classification of fundal types graded as to sclerosis and retinopathy. He found that arteriolosclerosis was of greater

prognostic value than other retinal signs, patients with more sclerosis having poorer operative results. Gans expressed the opinion that in some cases more sclerosis developed after surgical treatment. Retinopathy disappeared in all his patients who had it prior to surgical intervention, although some vascular spasm remained. Peet and Isberg<sup>39</sup> also found that patients who had only retinal arteriolosclerosis usually had the poorest operative results and they expressed the belief<sup>40</sup> that patients with retinal hemorrhages had an appreciably shorter postoperative life span than those without retinal hemorrhages. In a recent communication, Smithwick<sup>52</sup>, who has reclassified all his patients to conform to the Keith-Wagener grouping<sup>59</sup>, found a significantly better prognosis in the patients who underwent operation than in the control group.

Hammarström<sup>23</sup> followed 103 patients who had undergone operation with comprehensive studies. He noted regression or complete disappearance of retinopathy in all 22 Group III and IV patients who were still alive 4 months to 6 years after operation. All except 4 of these had a good lowering of blood pressure. In 2 Group II patients retinal exudates developed in the immediate postoperative period. There was a significantly better prognosis for Group III and IV patients who underwent operation than in the medically treated Keith-Wagener control series.

Cohen<sup>9</sup> reported a series of 90 patients with hypertension, 85 of whom underwent sympathectomy. Of the 85, 23 were said to have had normal eye-grounds both before and after operation, and 21 (91%) of the 23 had good general surgical results. Mild changes were said to have been present in 42, moderate in 18 and severe in 2. Good results were obtained by surgical treatment in 88% of the patients with mild retinal lesions, in 72% of those

with moderate lesions, but in none of those with severe lesions. Apparently all of these 3 groups included patients with retinopathy. No patients showed postoperative progression of ocular lesions and in 22 cases the hemorrhages, exudates and papilledema disappeared. In discussing Cohen's paper, Hinton<sup>25</sup> stated that he had had good operative results in 4 patients with Group IV fundal changes but with no cardiac or renal lesions. However, in patients with other organs involved in addition to neuroretinopathy, he felt that chances for improvement were minimal.

Many observers have expressed the belief that surgical treatment for hypertension is contraindicated in patients with papilledema (Group IV). The percentage of good results in this group is very low, according to Ayman and Goldshine<sup>2</sup>, Bedell<sup>5</sup>, L. Weekers<sup>62</sup>, R. Weekers<sup>63</sup>, de Takats and associates<sup>54</sup>, Govaerts<sup>21</sup>, Bartels and associates<sup>3</sup>, Wagener, Cusick and Craig<sup>61</sup>, and King<sup>32</sup>. For instance, Govaerts reported that all Group IV patients on whom he had operated were dead within 14 months after operation. On the contrary, Ray<sup>46</sup>, Crile and Crile<sup>12</sup>, Hinton and Lord<sup>26,27</sup>, and Luzuy and Porge<sup>33</sup> expressed the opinion that the results in many Group IV patients are sufficiently good to warrant operation, and Poppen and Lemmon<sup>44</sup> stated that these patients should undergo operation as soon as possible. Gilchrist<sup>20</sup>, Wilson<sup>64</sup> and Cooke<sup>10</sup> found that Group IV patients almost always had improvement in the retina. They noted that there is definitely a better prognosis following sympathectomy even though the blood pressure remains high. Peet and Isberg<sup>39</sup> pointed out that 19% of 112 surgically treated Group IV patients in their series were alive 5 to 11 years after operation as against 1% of the Keith-Wagener-Barker control series. Bassett<sup>4</sup> declared

that 21.6% of his 143 Group IV patients survived 5 to 11 years after sympathectomy, and he expressed the opinion furthermore that patients with preoperative cerebrovascular accidents were materially protected by surgical treatment against other such accidents.

Table 1 is constructed from the data presented by Evans and Bartels<sup>15</sup> (173 patients observed for from 6 months to 3 years), by Bartels, Poppen and Richards<sup>3</sup> (54 cases), by Poppen and Lemmon<sup>44</sup> (100 cases), by Woods and Peet<sup>65</sup> (60 cases observed more than 9 months), by Palmer<sup>37</sup> (64 cases observed for 3 years), by Wagener, Cusick and Craig<sup>61</sup> (121 cases observed for from 1 to 60 months) and by Hollenhorst<sup>28</sup> (95 cases observed for from 6 to 24 months). All of the patients were classified preoperatively according to the Keith-Wagener grouping. It can be noted that there is considerable variability in the percentage of successes and failures in each group. However, it can be noted also that there is a definite tendency toward lessening of successful results and increase of failures as the cases progress in classification from Group I to IV.

TABLE 1. PERCENTAGE RANGE OF RESULTS REPORTED IN VARIOUS SERIES OF SYMPATHECTOMIES FOR HYPERTENSION

|           | Good results<br>% | Fair results<br>% | Poor results<br>% |
|-----------|-------------------|-------------------|-------------------|
| Group I   | 25 to 83          | 16 to 75          | 0 to 42           |
| Group II  | 22 to 55          | 16 to 40          | 0 to 52           |
| Group III | 0 to 48           | 28 to 64          | 13 to 63          |
| Group IV  | 0 to 44           | 0 to 44           | 12 to 100         |

A number of studies of the ocular fundi preoperatively and postoperatively have been made, though not all of them include complete studies of the vascular lesions. The first report in the literature is that of one of us (H. P. W.)<sup>27</sup> in 1931. A boy, aged 10 years, was submitted to cervicothoracic ganglionectomy in a vain attempt to

benefit a severe retinopathy due to malignant hypertension. No postoperative change in the vessels nor in the retinopathy was noted.

There have been numerous case reports of the dramatic improvement noted in the retinas of patients after sympathectomy. Most of these reports were of patients suffering from malignant hypertension. McKeown<sup>34</sup>, Tiscornia<sup>55</sup>, Introzzi<sup>29</sup>, Euler<sup>14</sup>, Rycroft<sup>48</sup>, Stephenson<sup>53</sup>, Heuer and Glenn<sup>24</sup>, Philips<sup>13</sup> and many others have reported single cases or small series of cases to show postoperative improvement in vision, vasospasm, retinopathy and neuroretinopathy, some with and some without simultaneous improvement in the general condition of the patient. Ray<sup>46</sup> stated that hemorrhages and papilledema always improve after surgical treatment even though the level of blood pressure may not be materially lowered.

Page and Heuer<sup>36</sup>, after section of the anterior nerve roots, noted relaxation of spasm of the retinal arterioles in 11 of 17 cases, absorption of exudate in 2, disappearance of papilledema in 3 and secondary glaucoma in 1. Allen and Adson<sup>1</sup> reported disappearance of retinopathy and arteriolar spasm in patients who showed clinical improvement. Craig and Brown<sup>11</sup> performed splanchnicectomy on 2 patients with retinopathy. After 3 months, 1 patient showed a drop in blood pressure, a disappearance of retinopathy and a widening of the retinal arterioles, but the other patient showed no change either of blood pressure or of the retina.

The first large series of cases reported was that of Fracliek and Peet<sup>16</sup> in 1936. Ninety patients with essential hypertension underwent supradiaphragmatic splanchnicectomy; 36 were followed for from 5 to 22 months. No attempt was made to grade the vascular changes in the retina. Only the

extent of the retinopathy was described. Improvement was noted in the retinas of only 3 of 18 patients who had a good postoperative drop in blood pressure. Patients whose blood pressure remained high showed no retinal improvement except 1 patient whose papilledema disappeared postoperatively. Two patients with neuroretinopathy and 1 with angiospastic retinopathy showed good general improvement and clearing of the retinal lesions following operation.

In 1939, Wagener, Cusick and Craig<sup>61</sup> made detailed studies of the retinas of 32 patients before and after rhizotomy or subdiaphragmatic splanchnicectomy, and reported on the ophthalmoscopic examinations of a total of 121 patients who underwent operation. Their findings will be noted later in this paper, compared with a similar group treated by the Smithwick procedure<sup>28</sup>.

Tooke and Nicholls<sup>56</sup> observed 15 patients whom they diagnosed as having malignant hypertension although 37% were said to have had normal ocular fundi. After splanchnicectomy, 1 patient of the group had more marked fundal and general findings, 1 was unchanged, while the remainder were said to have been improved from every standpoint including that of the ocular fundi. Evaluation of the ocular status is difficult in this series.

Puig Solanes<sup>45</sup> did ophthalmoscopic examinations on 18 patients on whom operation by the Smithwick technique<sup>61</sup> was performed. Apparently 5 of his patients had malignant hypertension and 7 more were of the chronic progressive type. Of 8 patients examined 4 to 14 months after operation all had persistent arteriolar narrowing but had a diminution of focal constrictions and a disappearance of retinopathy. There was immediate postoperative increase in spasm and retinopathy in half of Puig Solanes' patients. He expressed

the belief that the retinal changes were independent of the blood pressure levels or of the general condition of the patient, but that similar vascular changes occurred in other organs, particularly the brain.

Tuckwell<sup>57</sup> found that neuroretinopathy disappeared in all 13 Group IV patients who underwent operation, but noted that 1 patient had returned to Group IV 3 years later. Of his 6 patients with Group III eyegrounds, 3 regressed to Group II, 1 remained in Group III and 2 advanced to Group IV. In 1 patient without retinopathy papilledema developed 1 year and in another 3 years after operation. A deterioration of the retinal condition was invariably accompanied by continued or heightened elevation of the blood pressure. King<sup>32</sup> could see little improvement in the fundal condition of several Group 4 patients whom he followed. Morgan<sup>35</sup> reported on 1 young patient who had a closure of the central retinal artery of one eye on the first postoperative day. Smithwick<sup>50</sup> found improvement of the retinas in all patients with papilledema and in 75% with retinopathy. He also noted the disappearance of arteriovenous compression in many cases.

It is obvious that, generally speaking, the response of the retinal lesions to splanchnic resections is favorable. If we combine various series reported by Evans and Bartels<sup>15</sup> (117 cases), Peet, Woods and Braden<sup>42</sup> (219 cases), Woods and Peet<sup>65</sup> (76 cases), Peet and Isberg<sup>39</sup> (146 cases), Wagener, Cusick and Craig<sup>61</sup> (32 cases) and Hollenhorst<sup>28</sup> (45 cases), data are available on a total of 613 cases. After operation, the retinal lesions improved in 406 (66%) remained unchanged in 185 (30%), and increased in 22 (4%). Included in these cases were 77 instances of retinopathy with papilledema reported by Peet and his collaborators and by Evans and Bartels.

Retinopathy of this type improved in 73 (94.8%). The papilledema receded completely in 40 (55%) of the 73 cases. Peet, Woods and Braden<sup>42</sup> stated that, if papilledema receded completely, it never returned, no matter how long the patient survived.

The statements by Gans, Gibson and others with reference to the prognostic significance of retinal arteriosclerosis are supported by the results obtained in a series of 95 patients whom one of us (R. W. H.)<sup>28</sup> has studied before and after combined supradiaphragmatic and infradiaphragmatic sympathectomy and splanchnicectomy. Forty-three of these patients were re-examined ophthalmoscopically 6 to 24 months after operation. It was found that only a low percentage of patients with high grades of sclerosis were benefited by surgical treatment. The proportion of good results in this series dropped from 56.7% in those with minimal sclerosis to 0% in those with severe grades, while the percentage of failures rose from 23.3% to 66.7% as increasing sclerosis was present in the retinal arterioles. Patients with postoperative improvement in vasospasm showed good results in 59.3%, fair in 18.5% and poor in 22.2% of cases.

Sixty of the patients in this series did not have retinopathy prior to operation. It is of interest that 19 of these were found to have cottonwool patches in the retinas at the first postoperative ophthalmoscopic examination made within 10 days after the second stage of sympathectomy. No explanation for this could be found. Among this group, 9 patients were observed to have ultimate good results, 2 fair and 8 poor results. Only 9 of these patients returned for re-examination 6 to 18 months after operation. None of them had retinopathy. However, of the 19, 1 patient had died after 17 months, 1 had had several cerebral angiospastic episodes and 2 had had hemiplegia.

Among the 41 patients who were observed to have no onset of retinopathy during the immediate postoperative period, only 1 had an episode of mild transient hemiparesis and there were no deaths.

In 5 of the 22 patients who had retinopathy without papilledema (hypertension Group III) an increase in retinopathy developed immediately after the second stage of operation. Two of the 5 were re-examined 7 months after operation. One still had active retinopathy and had received no benefit from the operation; the other had had a good postoperative course and there was no retinopathy. It was learned through correspondence that 1 of the other 3 patients had died; 1 had had a good result, had gone through a pregnancy and had been delivered of a normal child with no difficulty, and the third had had a fair result. There were no deaths nor cerebrovascular episodes in the 17 Group III patients whose eyegrounds remained the same or improved in the immediate postoperative period.

Of the 10 Group 4 patients who underwent operation, 4 were re-examined 6 to 20 months later. Three had no papilledema and no retinopathy; 1 still had mild papilledema 10 months after operation and was unimproved by the surgical procedure. Of the 3 patients with retinal healing, fair results were obtained in 2 patients. The third patient had a good postoperative result and had a final average diastolic pressure less than 100 mm. of mercurv.

In this series, 11 of 13 Group III patients and 3 of 4 Group IV patients had a complete disappearance of retinopathy on their final examination. However, among the 14, 4 were classified as operative successes, 4 as fair results and 6 as failures. When the vascular changes irrespective of the retinopathy were noted, it was found that the vessels were unchanged in 5

(83%) of the 6 failures and improved in 1, while of the 4 good results the vessels were unchanged in 1 and improved in 3. This appears to indicate that the grade of generalized and localized spastic constrictions persisting in the retinal arterioles is much more sensitive as an indicator than is the presence or absence of retinopathy in the postoperative period.

In this connection a recent report by Peet and Isberg<sup>41</sup> is of considerable interest. They studied 28 hypertensive women treated by splanchnicectomy who later became pregnant. Ten of these patients who had had angiospastic retinitis before operation, 1 with papilledema, had normal blood pressures after operation. Nine of these patients, including the 1 who had had papilledema, were delivered of normal children without complications and only 2 had a slight rise in blood pressure following pregnancy.

The one paper in the literature which lends itself fairly well to comparison with subsequent work is that of Wagener, Cusick and Craig<sup>61</sup>. The results that they reported for patients who underwent rhizotomy or subdiaphragmatic sympathectomy are not nearly so favorable as those reported by subsequent investigators. In the series of one of us (R. W. H.) as well as in the foregoing paper there is a sharp increase of good results as the degree of arteriolosclerosis diminishes. In the earlier series it was found that the proportion of good results from sympathectomy dropped from 40% in those without arteriolosclerosis to 9% in those with marked vascular sclerosis, while in the second series this range is from 56.7% to 0%. In the original series the proportion of failure increased from 20% in the group without arteriolosclerosis to 82% in those with marked changes. In the later series this range was from 23% to 66.7%. Wagener and associates

reported no successes in 7 Group 4 patients while in the recent group there were 2 successes and 2 fair results in 10 patients. Furthermore, in the earlier series there was immediate postoperative onset of retinopathy in one sixth of the patients, while this occurred in one third of the recent group.

If the average results obtained in a large series of cases are considered, prognostication by examination of the retinal changes seems to be reliable. However, it is difficult to evaluate an individual patient accurately. In spite of the presence of severe retinal changes a satisfactory postoperative drop in blood pressure and more or less complete alleviation of headache or other symptoms may be obtained. On the other hand a patient with only insignificant lesions in the retina may obtain little or no relief from operation. Thus, the percentage chance of a successful result for the patient can be estimated by the grade of retinal arteriolosclerosis and angiospasm and by the presence or absence of retinopathy or neuroretinopathy. However, as Gibson<sup>18</sup> remarked, it cannot be stated dogmatically that the patient will obtain a good, fair or poor result. The cardiac, renal and cerebral status must also be noted, and the lability of the blood pressure must be determined. The most recent compilation of the criteria for evaluating the suitability of a patient for surgical therapy is that of Scoville and Post<sup>40</sup>. It is based on considerations of age, sex, heredity and symptoms, on the magnitude, type and variability of the patient's blood pressure, and on the pathologic changes associated with the elevated blood pressure as manifested in the heart, kidneys, brain and eyes. Much the same indications and contraindications are listed by most authors to a greater or lesser degree. Hammarström<sup>23</sup> has expressed the opinion that patients



with retinopathy must have good renal function to warrant sympathectomy.

It is generally conceded that patients with hypertensive retinopathy with papilledema receive on the whole the least benefit from surgical treatment of hypertensive cardiovascular disease, while patients with low degrees of retinal arteriolosclerosis and marked tonic or spastic arteriolar changes derive the greatest benefit statistically. Consequently, a patient with high degrees of arteriolosclerosis should not be urged into operation and must be warned of the poor prognosis for satisfactory lowering of the blood pressure even though much alleviation of symptoms of headache, dyspnea or nervousness may be obtained. Patients with papilledema, except those associated with low degrees of arteriolosclerosis, also must be given a poor prognosis as to improvement in blood pressure. Their lives seem to be prolonged by sympathectomy, however.

Patients who have poor vision as the result of retinopathy can usually be assured that their vision will improve postoperatively even though their general condition may not follow suit. From this standpoint alone operation may be considered as justified in a small group of patients, since spontaneous regression of hypertensive retinopathy, while it occurs occasionally<sup>30</sup>, probably is not as frequent and complete as in postoperative Group III and IV patients. Furthermore, in some cases the improvement of vision is very rapid, even taking place while the patient is still in the hospital recovering from the operation. There are, however, only a few available reports on the visual end results in hypertensive retinopathies under medical management.

The method of production of retinal changes in patients afflicted with hypertension is still unknown. The cause of essential hypertension is

almost equally obscure. In most cases, however, both vasospastic and organic changes in the arterioles seem to be present. Possibly, the vasospastic constriction is brought about through a humoral factor elaborated elsewhere in the body, most likely in the kidneys. The disappearance of active spasm of the retinal arterioles and the regression of retinopathy following sympathectomy are difficult to explain. It is obvious that these changes are not due to a direct neural effect on the retinal vessels (Wagener<sup>28</sup>, Gans<sup>17</sup>). They must be due to an alteration in the systemic vasomotor balance resulting from dilatation of the large vascular bed of the abdominal organs and the removal of a possible vasoconstrictor clamp to the kidneys. The latter may lessen the amount of humoral substance liberated into the blood stream and thus permit relaxation of the retinal arterioles and allow gradual absorption of the retinal edema.

Thus, to recapitulate, ophthalmoscopic examination of the ocular fundi of patients with hypertensive cardiovascular disease should be directed not only toward the presence or absence of hemorrhages, cottonwool patches and edema of the retina and optic disk, but should include a meticulous grading of the degree of arteriolosclerosis, angiospasm and tonic narrowing of the arterioles. Since the degree of benefit obtained from surgical therapy seems rather definitely to be in inverse ratio to the degree of organic retinal vascular change, it is important that ophthalmoscopic examination be included in the studies used for the preoperative evaluation of such patients. It must be emphasized that no retinal changes can be construed as being an absolute contraindication to sympathectomy, but the presence of the higher degrees of sclerosis and of retinopathy with papilledema reduces the probability of obtaining a good result.

## ADDENDUM

Kempner (N. Carolina Med. J., 6, 117, 1945) presented photographs of the fundi of 15 patients taken before and after several weeks of subsistence on the rice diet. He stated that in 21 of 33 patients "the retinopathy improved greatly or even cleared up completely under the rice regimen."

Craig (J. Am. Med. Assn., 139, 1239, 1949) stated that preoperative classification of patients according to the Keith-Wagner groups is important in the evaluation of the results of surgical treatment of hypertension. If, under observation, the condition of a patient is noted to progress to a higher group, operation will have its most beneficial effect if it can be carried out shortly after the increase in severity of the hypertensive disease has occurred.

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# BOOK REVIEWS AND NOTICES

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ON THE CONTRIBUTIONS OF HUGH OWEN THOMAS OF LIVERPOOL, SIR ROBERT JONES OF LIVERPOOL AND LONDON, JOHN RIDLON, M.D., OF NEW YORK AND CHICAGO TO MODERN ORTHOPEDIC SURGERY. By H. WINNETT ORR, M.D., with a Supplement on RIDLON AND HIS SHARE IN MOULDING ORTHOPEDIC SURGERY. By ARTHUR STEINDLER, M.D. Pp. 253; 22 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, \$4.50.

Dr. Orr has presented the profession with a wealth of accumulated material regarding the impact that the principles of Thomas, Jones and Ridlon have made on orthopedic surgery. It is obviously a labor of love that has motivated him. Those students of orthopedic history will find in this small book much of interest to them on the treatment of diseases of the bones and joints.

Dr. Steindler's added chapter on Dr. Ridlon's contribution has an especially valuable personal touch and adds to the value of this very interesting book. P. C.

DISCOVERERS FOR MEDICINE. By WILLIAM H. WOGLON, M.D. Pp. 229; 14 ills. New Haven: Yale University Press, 1949. Price, \$3.75.

A series of some of the most important historical events in the development of medical science are written in a clear, easily understandable style for popular scientific reading. Essentially, the text considers the numerous medical discoveries that have been made by individuals unrelated to the medical profession. Some of the outstanding chapters deal with such subjects as Mendel's revelations of botanical heredity, the X-ray, Metchnikoff's conception of the importance of phagocytosis as a defense mechanism, blood pressure measurements, respiration, vaccination, and the discovery of digitalis. Not only are these discoveries clearly explained, but also much of the life histories of the discoverers, as well as the circumstances that led them to findings of such great medical importance. I. Z.

PUBLIC HEALTH IN THE WORLD TODAY. Edited by JAMES STEVENS SIMMONS, Dean, Harvard School of Public Health, and IRENE M. KINSEY. Foreword by JAMES BRYANT CONANT. Pp. 332; 17 ills. Cambridge, Mass.: Harvard Univ. Press, 1949. Price, \$5.00.

With the great expansion in the concept and practice of "Public Health" that has occurred in recent years, and the increasing importance of this recently developed field for our community existence, the title of this book will obviously stimulate further consideration. The subjects of the 24 articles and the names of the 24 distinguished experts who contributed them should suffice to invite many to seek closer acquaintance with the contents. Based on a successful series of weekly lectures sponsored by the Harvard School of Public Health, the book presents a comprehensive and authoritative statement of the public health problems, aims and accomplishments in mid 20th century. Public health experts will want this book for its content of authoritative facts and thought stimulating discussions; many non-professionals concerned with the health of the world from political, sociological and esthetic points of view may find in it even more profitable reading. E. K.

VIRAL AND RICKETTSIAL INFECTIONS OF MAN. Edited by THOMAS M. RIVERS, M.D., The Rockefeller Institute for Medical Research. Pp. 587; 77 ills., 6 in color. Philadelphia: J. B. Lippincott, 1948. Price, \$5.00.

This excellent volume fills an important gap in medical literature. Our understanding of viral and rickettsial diseases has progressed so rapidly in the last twenty years that often textbooks have been badly out of date by the time they got into print. Greater stability of ideas during the past few years has enabled Dr. Rivers and his collaborators to get together a book whose essential information seems to be fundamental and will probably not require serious alteration.

Chapters are devoted to the physical, chemical, and serological features of viral and rickettsial diseases, chick-embryo and tissue culture techniques, and epidemiological studies. Following this the various diseases are considered singly or in closely related groups. The individual authors are all well qualified to speak with authority. Adequate bibliographies accompany each chapter.

Technically the book is attractive. Well printed on heavy glossy paper, the illustrations are excellent. A subsidy from the National Foundation for Infantile Paralysis has been used to reduce the price. This book

is a companion to "Bacterial and Mycotic Infections of Man" edited by René J. Dubos. W. S.

**THE PHARMACOLOGIC PRINCIPLES OF MEDICAL PRACTICE.** By JOHN C. KRANTZ, JR., Prof. of Pharmacology, School of Medicine, Univ. of Maryland, and C. JELLEFF CARR, Assoc. Prof. of Pharmacology. Pp. 980; 95 ills. Balt.: Williams & Wilkins, 1949. Price, \$10.00.

This is a text book of pharmacology designed primarily for medical students taking courses in that subject. It differs from most other works in the field in that more space and attention is given to therapeutics. This will undoubtedly serve to interest the student and to unify the curriculum, but it has the disadvantage of an extreme brevity which results in the oversimplification of many therapeutic problems.

The full-page illustrations of prominent pharmacologists, both living and dead, accompanied by characteristic quotations from their works, and the short appendix on the discovery and evaluation of new drugs, are interesting features of the book, which is clearly written, although the style, a multitude of short sentences, is not pleasing to the Reviewer.

This useful compilation is strictly up-to-date, and without doubt will be popular with medical students and with the increasing number of physicians seriously interested in the way their therapeutic efforts affect the human body. I. S.

**BIOCHEMICAL EVOLUTION.** By MARCEL FLORKIN, Univ. of Liège. Edited, translated, and augmented by SERGIUS MORCULIS, Univ. of Nebraska. Pp. 157; 25 figs. New York: Academic Press, 1949. Price, \$4.00.

Using the systems of zoological classification of animals, as established by the morphologists, the author proceeds to develop the evidence for a series of systematic biochemical characteristics as well. One is concerned with the comparisons of biochemical constituents and of the biochemical systems as they are found in the various species of the animal kingdom. Similarities and dissimilarities are noted. The evolution of biochemical systems and adaptations are traced under the main headings of milieu interieur, respiratory function, hydrolytic processes of digestion, nitrogen metabolism, photoreception, and osmoregulation. The systematic biochemical characteristics of the vertebrates, tunicates, cyclostomes, elasmobranchs, sipunculids and insects are discussed, with a final chapter on perspectives concerned with the mechanism and the reversibility and irreversibility

of biochemical evolution. These data, so cogently presented, offer strong support for the quotation from J. B. S. Haldane that "Our final theory of evolution will see 'it largely as a biochemical process.'" H. V.

**EARLY RECOGNITION OF DISEASE.** Edited by SIR HENEAGE OGILVIE, K.B.E., and WILLIAM A. R. THOMSON, M.D. Pp. 134. London: Eyre & Spottiswoode, 1949. Price, 10s.

This book, one of "The Practitioner" Handbooks series, consists of 14 chapters, each written by an author well qualified to discuss an assigned subject—such as, for example: heart disease, neurological disease, diseases of the eye, mental disorders, the complications of pregnancy.

Each author has made a commendable effort to present in brief form a discussion of the "early" symptoms of the diseases in his allotted field, and their significance. The trouble is the question of what is truly an early symptom. The several authors have, as might be anticipated, approached this problem in different ways; some discuss many symptoms such as the vomiting of half a pint of blood which surely needs no emphasis as an early symptom; others emphasize minor symptoms which would scarcely bring a patient to a doctor but whose significance would be of great importance to the patient if this information could be brought to his attention.

In other words much of the book should not be needed by any well-trained doctor, but it would be of great value either to second rate doctors who unfortunately are the very ones who probably will not read it, or to the laity for whom it is not written.

The book is a worth-while effort in a most difficult direction. O. P.

**NATURAL PRODUCTS RELATED TO PHENANTHRENE.** By LOUIS F. FIESER and MARY FIESER, Harvard University. 3d ed. Pp. 704. New York: Reinhold, 1949. Price, \$10.00.

This new edition is a splendid, up-to-date, and authoritative book on an important subject basic to the medical sciences. It is twice as large as the previous edition. The main subjects covered are as follows: the morphine alkaloids and morphine substitutes, resin acids, sterols and bile acids, vitamin D, sex hormones, adrenal cortical hormones, cardiac glycosides, saponins, steroid and terpenoid alkaloids, and steroid metabolism. The main changes from the 2d edition are of interest chiefly to chemists, namely, the omission of the chemistry of polycyclic hydrocarbons (including carcinogens) and the addition of

a chapter by Richard B. Turner on the stereochemistry of the steroids.

In the 12 years since the appearance of the 2d edition, great advances have been made not only in the chemistry but in the metabolism, pharmacology, physiology and clinical implications of these types of compounds. The biological aspects are treated in considerable detail; this makes the book of wide interest and value to investigators in medicine and allied sciences.

The reviewers know of no other book on the subjects covered that combine in such happy fashion the well-known ability of the Fiesers to unearth the facts of a complicated chemical subject and to present them in a style that is orderly and eminently readable.

J. H.; M. S.

**HISTOLOGY AND HISTOPATHOLOGY OF THE EYE AND ITS ADNEXA.** By I. G. SOMMERS, M.D., Ass't Prof. Ophthalmology, College of Medical Evangelists. Pp. 784; 69 ills. New York: Grune & Stratton, 1949. Price, \$12.00.

THIS is a welcome addition to our texts on this subject. No satisfactory work has appeared in English since Parsons' "Pathology of the Eye" and that is now long out of date and out of print. This text covers the normal histology, embryology and senescence of the eye, its general pathology and the more detailed pathology of its several parts. There is even a chapter on the pathology of the surgery of the eye.

A good bibliography is found at the end of each chapter and rather interesting notes under the caption "Reading of Source Material" in which the author abstracts the findings of various case reports.

The illustrations are good, and the type and format of the book are excellent. F. A.

**CARDIAC CATHETERIZATION IN CONGENITAL HEART DISEASE.** By ANDRÉ COURNAND, M.D., Assoc. Prof., Columbia Univ., JANET S. BALDWIN, M.D., Ass't Prof., New York Univ., and AARON HIMMELSTEIN, M.D., Instructor, Columbia Univ. Pp. 108; illustrated. New York: Commonwealth Fund, 1949. Price, \$4.00.

This monograph is divided into 2 parts. Part one describes and discusses the equipment, techniques and methods used in a well-equipped and well-organized laboratory for performing cardiac catheterization on patients with congenital heart disease. Formulas for calculating intracardiac shunts are included. In part two are presented 17 illustrative cases with correlation of the clinical and physiological data. Emphasis is placed here on the acyanotic group of congenital heart lesions.

The presentation of the subject is concise, yet sufficiently complete, and reflects the authors' long experience and thorough knowledge of this subject. Illustrations are adequate in number and quality.

It seems to the reviewer regrettable that the authors have chosen to limit the presentation of case material almost exclusively to the acyanotic group of congenital heart lesions. The value of the book would have been enhanced had more cases from the cyanotic group been included. Much the same criticism can be made about the failure to include the chest leads in the electrocardiograms. With these exceptions, the work is well done and is recommended to those interested in congenital heart disease. R. K.

**THE TEMPORAL BONE AND THE EAR.** By THEODORE H. BAST, Ph.D., Prof. of Anatomy, Univ. of Wisconsin, and BARRY J. ANSON, Ph.D., Prof. of Anatomy, Northwestern Univ. Pp. 478; 166 ills., 30 in color. Springfield, Ill.: Charles C Thomas, 1949. Price, \$12.00.

THIS scholarly monograph is based to a very large extent upon original research by the authors. It brings together and summarizes material which has previously appeared in numerous scientific articles. The book is profusely illustrated with drawings and photomicrographs, a number in color. Each of the 9 chapters in the book is followed by a bibliography. An index of authors and a general subject index complete the volume.

The monograph is primarily descriptive anatomy and embryology. Matters of function and consideration of theories of hearing are to be found in the last chapter, together with a historical survey of the same. The present monograph supplies a long-felt need for a detailed consideration of these regions, as the internal ear and temporal bone are so complex that no ordinary textbook of anatomy can do justice to them. W. W.

**OPERATIVE SURGERY.** By FREDERICK C. HILL, M.D., Assoc. Prof. Surgery, The Creighton Univ., School of Medicine. Foreword by CHARLES W. MAYO, M.D. Pp. 698; 255 ills. New York: Oxford University Press, 1949. Price, \$12.75.

As stated in the preface, this volume has been written for the intern, resident and less experienced surgeon. Most of the operations of general surgery, orthopedics and gynecology have been briefly described, and some have been illustrated. No historical data are given, and there are no references.

In the opinion of this reviewer, most surgeons expect their men in training to know

more about most operations than is described or illustrated in this book. Except for brief glances at the essentials of a technique before operating, the value of the book appears limited. The artists are to be commended for their unusually fine illustrations. C. K.

**THE HORMONES.** Edited by GREGORY PINCUS, Worcester Foundation, and KENNETH V. THIMANN, Harvard Univ. Vol. I. Pp. 886. Illustrated. New York: Academic Press, 1948. Price, \$13.50.

This is the first of 2 volumes devoted to a comprehensive review. To quote from the preface, this volume "contains the chemistry of the hormones, the role of hormones in organisms other than mammals, and some aspects of the animal physiology. The second volume will contain the bulk of the mammalian endocrinology proper, with clinical applications." The 16 chapters represent the contributions of 14 authoritative investigators. The hormones of plants, insects and crustaceans are considered in detail. Other chapters deal with the internal secretions of the gastro intestinal tract, parathyroids, pancreas, anterior pituitary, adrenal cortex, ovary and testis, and the hormonal control of lactation and mammary growth.

There is some variation in the quality and style of the text, as is inevitable in such a collaborative effort. Chief emphasis is placed upon chemistry, assay and extraction techniques and experimental physiology. This book will constitute an important work of reference in its field, even after the rapid march of endocrine chemistry and physiology has necessitated the compilation of supplementary data in similar form. The publication of the 2d volume will be awaited with interest. E. R.

**LEHRBUCH DER EMBRYOLOGIE.** Von WALTER BRANDT, M.D., Ph.D., früher Prof. der Anatomie, Univ. Köln. Pp. 648; 472 ills. Basel, Switzerland: S. Karger, 1949. Price, S.Fr. 56.

IN this clearly written and well constructed volume in German, Professor Brandt has summarized recent work in experimental embryology and incorporated it into a book that will be useful to many, including students who desire to improve their scientific German. In Part 1, a general survey of development is given, including a brief comparative embryology of lower forms with an account of work on amphibians, much of it by the author. This introduces much that is quite recent on human development, but regrettably not including the latest work of Dr. G. L. Streeter on developmental horizons. This part is written with the needs of medical students in mind,

with emphasis on developmental physiology and endocrinology, and on the relation of fetus to mother.

In Part 2, the development of organ systems is discussed, with 83 pages devoted to circulatory organs, 104 to digestive and respiratory organs, 67 to the genito-urinary system, and 105 to the nervous system. While the reviewer was impressed by the breadth of this work, which covers a very wide field, he would have welcomed a collected bibliography, to supplement the legends of the illustrations. A good index completes this stimulating textbook. S. W.

**HISTOPATHOLOGY OF IRRADIATION FROM EXTERNAL AND INTERNAL SOURCES.** Edited by WILLIAM BLOOM, M.D., Prof. of Anatomy, Univ. of Chicago. Pp. 808. Illustrated. New York: McGraw-Hill, 1948. Price, \$8.00.

This volume is a summary of the wartime work on the histological effects of radiation by the Histological Group of the Health Division, Metallurgical Laboratory of the University of Chicago. It is IV-221 of the National Nuclear Energy Series, a series expected to reach 60 volumes, reporting the declassified portions of work under the Manhattan Project.

The book describes the histological and cytological effects of total body irradiation from external (Roentgen-rays, gamma-rays, beta-rays, fast and slow neutrons) and internal (alpha, beta, and gamma-emitting substances) sources. The effects of the various forms of irradiation on the major tissues and organs are compared. Most of the experiments were done upon mice and rats, a few upon rabbits and guinea pigs. A great deal of new and valuable information is reported. Because of wartime haste and shortage of trained personnel, many categories are incomplete or need repetition.

The book is prolifically illustrated. Unfortunately a great many are bad, either out of focus, have poor contrast, or do not illustrate the desired feature. In a work of this kind this is a particularly serious flaw. Despite these faults the book is a necessary reference work for those working in this field. W. S.

**CAMPBELL'S OPERATIVE ORTHOPEDICS.** Edited by J. S. SPEED, M.D., and HUGH SMITH, M.D. 2d ed. In 2 Vols. Pp. 1633; Index Pp. 44; 1141 ills., 2 in color. St. Louis: C. V. Mosby, 1949. Price, \$30.00.

THIS 2 volume set is a monumental work to those interested in orthopedic surgery. The original one volume *OPERATIVE*

ORTHOPAEDICS compiled by the late Dr. Willis C. Campbell established the need and value for this type of book; in the present two volume set members of the Campbell Clinic and a few other outstanding contributors have produced again an excellent and enlarged work. All the contributors deserve congratulations. The book in the past and even more so in the present issue will continue to be of inestimable value to the young orthopedic surgeon in guiding him in the technical details of the various operative procedures and also to all practicing this specialty. It represents an amazing reference work and an encyclopedia of orthopedic knowledge. P. C.

DOCTORS OF INFAMY. By ALEXANDER MITSCHERLICH, M.D., and FRED MIELKE. Translated by HEINZ NORDEN. Pp. 172; 16 ills. New York: Henry Schuman, 1949. Price, \$3.00.

THIS is a well documented statement about the Nuremberg Medical Trials in 1946, the prosecution having been based entirely on captured documents. From the presentation it becomes apparent that the 23 S.S. physicians and scientists reacted to the pressure of distorted Nazi ideologies just as did many Germans in all walks of life. However, we must realize that members of our profession are especially blameworthy in so completely transgressing medical ethics as to commit the atrocities that were proved, even though it looks as if some of the scientists carried out their inhuman roles as a patriotic duty. The record makes strange and most unpleasant reading. E. K.

A PRIMER OF ELECTROCARDIOGRAPHY. By GEORGE E. BURCH, M.D., Henderson Prof. of Medicine, Tulane Univ., and TRAVIS WINSOR, M.D., Ass't Clin. Prof. of Medicine, Univ. of Southern California. 2d ed. Pp. 245; 265 ills. Phila.: Lea & Febiger, 1949. Price, \$4.50.

THE general form of the 1st edition has been retained (Reviewed in this Journal December 1945, p. 813). Among the more important additions are details of the mechanisms responsible for the patterns of infarction, and the substitution of unipolar for bipolar precordial leads. Seven instructive pages are given to the Intrinsic Deflection of the QRS Complex, *i. e.*, the record made on the instant at which the muscle below a unipolar electrode has been completely depolarized. The Reviewer echoes the authors' emphasis on the practical need of the beginning electrocardio-

grapher for mastering the 54 pages of Chapter 1, Principles of Electrocardiography. E. K.

## NEW BOOKS

*Veterans Administration Technical Bulletin.* Series 10. Vol. 2. Edited by PAUL B. MAGNUSON, Chief Medical Director. Pp. 55. Washington: U. S. Govt. Printing Office, 1948. No price given.

*Nutrition and the Soil.* By LIONEL PICTON, O.B.E. Introduction by JONATHAN FORMAN, F.A.C.A. Pp. 374. New York: Devin-Adair, 1949. Price, \$4.00.

*The British Encyclopaedia of Medical Practice With Cumulative Supplement*, 1949. Edited by Rt. Hon. LORD HORDER, G.C.V.O., M.D., B.Sc., F.R.C.P. Pp. 409 and 423 (Suppl.). London and Toronto: Butterworth, 1949. Price of complete set, 12 vols., \$139.50.

*The Common Form of Joint Dysfunction.* By WILLIAM KAUFMAN, Ph.D., M.D., Pp. 208; 34 figs. Brattleboro, Vermont: E. L. Hildreth, 1949. Price, \$8.75.

A PRESENTATION of the author's experiences in private practice with impaired joint mobility and the results obtained with adequate niacinamide therapy.

*János, The Story of a Doctor.* By JOHN PLESCH. Translated by EDWARD FITZGERALD. Pp. 579; 37 ills. New York: A. A. Wyn, 1949. Price, \$5.00.

THE autobiography of a noted Professor of Medicine whose full life brought contact with many of the greatest scientists and artists of our day.

*The Basic Neurosis.* By EDMUND BERGLER, M.D., Pp. 353. New York: Grune & Stratton, 1949. Price, \$5.00.

THE author aims to demonstrate that unconscious psychic masochism forms the basis for all types of neurosis.

*Obesity.* By EDWARD H. RYNEARSON, M.D., Assoc. Prof. of Medicine, Mayo Foundation, and CLIFFORD F. GASTINEAU, M.D., Fellow in Medicine, Mayo Foundation. Pp. 144; 9 figs. Springfield, Ill.: Charles C Thomas, 1949. Price, \$3.50.

THIS latest monograph of the American Lecture Series discusses in practical terms the etiology, physiology, and harmful effects of obesity and presents diets and other obesity therapy. Though the bibliography is limited to "articles easily obtained and read," it contains 422 items.

*Sexual Behavior: Normal and Abnormal.* By EUSTACE CRESSER, M.D., Pp. 295. New York: Roy Publishers, 1949. Price, \$3.75.



*The Uses of Penicillin and Streptomycin.* By CHESTER SCOTT KEEFER, M.D., Wade Prof. of Medicine, Boston Univ. School of Medicine. Porter Lectures, 15. Pp. 72. Lawrence, Kansas: Univ. of Kansas Press, 1949. Price, \$2.00.

*The Technique of Pulmonary Resection.* By RICHARD H. OVERHOLT, M.D., Clinical Prof. of Surgery, Tufts College Medical School, and LAZARO LANGER, M.D., Instructor in Surgery, Univ. of Cordoba. Pp. 205; 122 ills., 16 in color. Springfield, Ill.: Charles C Thomas, 1949. Price, \$8.00.

"This book is primarily a presentation of the technique of resection as used by the authors. Reference is made to alternate steps that we occasionally find to be helpful . . . The first part takes up technical matters that are common to any type of resection . . . The second part considers in some detail the anatomy of the lung itself as it applies to problems of dissection at the primary, secondary, and tertiary hilar levels . . . Each specific type of resection is then considered." (Foreword.)

*Mycoses and Practical Mycology.* By N. GOHAR, M.R.C.S. (Eng.). Foreword by SIR PHILIP MANSON-BAHR. Pp. 234; 134 ills., 4 in color. Balt.: Williams & Wilkins, 1948. Price, \$6.00.

A SOMEWHAT uncritical account of the mycoses. Written from the Egyptian point of view, the book is of correspondingly lessened value to American mycologists.

*Practical Lessons in Psychiatry.* By JOSEPH L. FETTERMAN, M.D., Director, The Fetterman Clinic, Cleveland, Ohio. Pp. 342. Springfield, Ill.: Charles C Thomas, 1949. Price, \$5.75.

*How to Become a Doctor. A Complete Guide.* By GEORGE R. MOON, A.B., M.A., Examiner and Recorder, Univ. of Illinois. Pp. 131. Phila.: Blakiston, 1949. Price, \$2.00.

*Oral Anatomy.* By HARRY SICHER, M.D., Prof. of Anatomy and Histology, Loyola Univ. School of Dentistry. Pp. 529; 310 ills., 24 in color. St. Louis: C. V. Mosby, 1949. Price, \$15.00.

THE author has attempted here to bring together as much of the descriptive anatomy of the human body as should prove useful to students of dentistry. He has tried to bridge the gap between theory and practice without going too deeply into matters of applied anatomy. The textbook is well illustrated and clearly written. It should prove attractive to many. W. W.

*Diagnosis of Viral and Rickettsial Infections.* Edited by FRANK L. HORSFALL, JR., M.D. Symposium, New York Academy of Medi-

cine, January 29 and 30, 1948. Pp. 153; 4 ills. New York: Columbia Univ. Press, 1949. Price, \$3.75.

THIS symposium consists of 13 chapters by 16 authors. The theory and interpretations of the diagnosis of viral and rickettsial diseases are discussed. Details of diagnostic procedures are not given. It contains profitable discussions for those interested in these fields. H. M.

## NEW EDITIONS

*Comparative Anatomy.* By LEVERETT A. ADAMS, Univ. of Illinois, and SAMUEL EDDY, Univ. of Minnesota. 2d ed. Pp. 520; 364 ills. New York: John Wiley & Sons, 1949. Price, \$5.00.

THIS book is intended primarily for college students but it will also serve very well as a handy reference. The text is divided into 2 parts. Part 1 defines the scope of the book and contains discussions of the theories of vertebrate ancestry, of the basic features of taxonomy, including in this descriptions of ancestral forms, and of the embryological development of the vertebrate egg. Part 2 is given to comparative anatomy and contains 12 chapters, each of which considers a separate system of organs or structures. The book ends with a list of about 150 references, most of which are in English, a glossary of 28 pages and an ample index. It is a competent presentation, written in a pleasant style, and is recommended to anyone whose interest takes him beyond the common laboratory animals. H. R.

*Textbook of Medicine.* Edited by SIR JOHN CONYBEARE, Physician to Guy's Hospital, London. 9th ed. Pp. 875; 23 ills. Balt.: Williams & Wilkins, 1949. Price, \$8.00.

*Food Poisoning.* By G. M. DACK, Ph.D., M.D., Prof. of Bacteriology. 2d ed. Pp. 184. Chicago: Univ. of Chicago Press, 1949. Price, \$3.75.

*Handbook of Materia Medica, Toxicology, and Pharmacology.* By FORREST RAMON DAVISON, Ph.D., Ass't Prof. of Pharmacology, Univ. of Tennessee Medical School. 4th ed. Pp. 730; 32 figs. St. Louis: C. V. Mosby, 1949. Price, \$8.50.

*Microbiology and Man.* By JORGEN BIRKELAND, Ph.D., Prof. of Bacteriology, Ohio State Univ. 2d ed. Pp. 525; 54 ills. Balt.: Williams & Wilkins, 1949. Price, \$5.00.

THIS is a continuation of the author's attempts to present general knowledge of microbiology as it concerns man. Six new chapters have been added, dealing with antibiotics, meningitis, foot and mouth disease, infections caused by spore-forming bacilli, air pollution and sanitation, and bacterial warfare. Taxonomic material has been deleted. Many new illustrations have been added, especially electron micrographs. This book will be found very good for college courses in microbiology. H. M.

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## ORIGINAL ARTICLES

### METASTASES IN BONE MARROW AND MYELOPHTHISIC ANEMIA FROM CARCINOMA OF THE PROSTATE\*

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THE tendency for carcinomas arising in certain organs to metastasize widely by way of vascular channels is notorious. The chief recipients of blood borne tumor fragments appear to be the lungs and the bone marrow<sup>14</sup>. In the lungs hematogenous metastases may result in nodular tumor growths, so-called lymphangitic carcinomatosis<sup>19</sup>, or tumor cell emboli which become organized as hyaline thrombi with the final lesion sometimes resembling pulmonary arteriosclerosis<sup>14,25</sup>. In the bone marrow the growth of neoplastic tissue leads to hematologic and to skeletal disease. Progressive anemia with immature granulocytes and nucleated red blood cells in the circulating blood, or occasionally anemia with hemolytic features, thrombopenia, or striking leukocytosis with granulocytic immaturity suggestive of leukemia are all well-known syndromes associated with neoplastic invasion of the bone mar-

row<sup>4,5,17,18,27,28,30,31,34</sup>. The well vascularized bones that contain red marrow are those predominantly affected by tumor metastases<sup>20</sup>. Lesions range from focal areas of disease to generalized skeletal devastation with varying amounts of bone destruction and proliferation.

The possibility of recognizing tumor metastases in the bone marrow by sternal puncture was first investigated by Rohr and Heggin<sup>21,22</sup>. In 75 patients with malignant tumors, 13 with proven bone metastases from bronchial, gastric, prostatic carcinomas or elsewhere, 11 were found to have tumor cells in films made from aspirated bone marrow. They divided the tumor cell types into small and large cell varieties. The former generally arose, they thought, from bronchial neoplasms and the latter from stomach or prostate. The tumor cells had no features by which the site of the primary tumor could be distinguished

\* Aided by grants from the Anna H. Hanes Fund and the Duke University Research Council.

with certainty. The demonstration of metastatic tumor cells by bone marrow aspiration was subsequently confirmed by many investigators<sup>8,9,15,16,17,26,29,33,35</sup>. The frequency of positive findings increased after Henning<sup>9</sup> suggested using bones other than the sternum and choosing the site for aspiration by the presence of tumor nodules, roentgen abnormalities, or areas of bone pain in the ribs, spinous processes, ilium, skull, and others. Franke<sup>8</sup> reported a very thorough study of a group of 134 patients with malignant neoplasms in whom bone marrow was obtained in this manner. Implants were found in the marrow of 20 of the 42 patients who had Roentgen-ray or pathologic evidence of bone metastases.

New developments in the chemotherapy of neoplasms, as well as the scant attention which English speaking authors apparently have given the above findings, made another study of tumor metastases in bone marrow appear worthwhile<sup>24</sup>. We have now made hematologic studies in 102 patients with various types of malignancies which had spread locally or produced distant metastases. Cellular implants diagnostic of metastatic tumor were found in 44. The present report deals with the 30 patients in this group who had carcinoma of the prostate gland. Neoplastic cells were demonstrated in the sternal marrow of 15 patients, and in the pelvic bones of two others. Marrow implants were occasionally demonstrated where there was no other evidence of metastasis. Anemia occurred in over half of the patients, and largely among those with metastases in whom it was related to the degree of marrow infiltration. Following castration and estrogen therapy amelioration of the anemia occurred in parallel with demonstrable regression of tumor infiltration in the bone marrow.

**Technical Procedures.** Bone marrow was routinely aspirated from the sternum with a No. 16 or No. 18 needle and films prepared directly from the tip of the needle on cover slips. When the sternal marrow was normal and metastases were suspected in deeply situated bones, about the acetabulum, vertebral bodies, and elsewhere, a long No. 18 spinal needle was implanted and its correct position verified by Roentgen-ray films before aspiration<sup>9,23,33</sup>. Often in bone marrows with neoplastic infiltration no more than a drop or two of sanguinous material could be obtained even with strong suction and rotation of the needle. When aspiration was unsatisfactory, a needle trephine<sup>32</sup> was used to remove a core of tissue after which the aspiration was repeated. The solid tissue obtained was fixed in Zenker's acetic acid dichromate solution, embedded in paraffin, sectioned and stained with Wright's, Giemsa's and routine stains. Blood and marrow films were stained with a buffered Wright's stain.

**Illustrative Case Reports.** CASE 1. W.D.W., B-93359, a 68-year old Negro farmer, was first seen at Duke Hospital on November 11, 1946, complaining of weakness, severe constipation and "aching in his bones." An unusual degree of constipation developed 4 or 5 years previously, became progressively worse, and for 4 or 5 months was nearly intractable. His desire for food slackened, and when he did eat he suffered lower abdominal pain. He lost weight finally to the amount of 50 pounds. During his last weeks at home, he was confined to bed by weakness and constant aching in his arms, chest, and low back.

Physical examination showed him to be a thin, senile, chronically ill, colored male. There were no palpable tumor masses. The superficial lymph nodes were not enlarged. There was moderately severe tenderness to pressure over the sternum. No abdominal organs or masses were palpable. By rectal examination there was no palpable tumor and on sigmoidoscopy there was no visible abnormality in the lower bowel. The prostate gland was described by a urologic consultant as being slightly enlarged, soft and tender without nodularity or induration.

A provisional diagnosis of carcinoma of the colon was made. A barium enema, however, showed no colonic abnormalities. Roentgen films made during this examination showed mottled sclerotic changes in the pelvic bones and vertebrae characteristic of metastatic carcinoma. Similar changes were subsequently demonstrated in the ribs.

Serologic tests for syphilis were negative. Urinalysis showed no abnormalities. Examination of the blood showed a severe anemia

with immature granulocytes and many nucleated red blood cells (Table 2). The red blood cells were conspicuously deformed and varied greatly in size and in shape. The blood

non-protein nitrogen was 35 mg. per 100 cc., the serum calcium 13.7 mg., and the serum phosphorus 3.3 mg. Two determinations of the acid phosphatase showed 16 and 23 King-

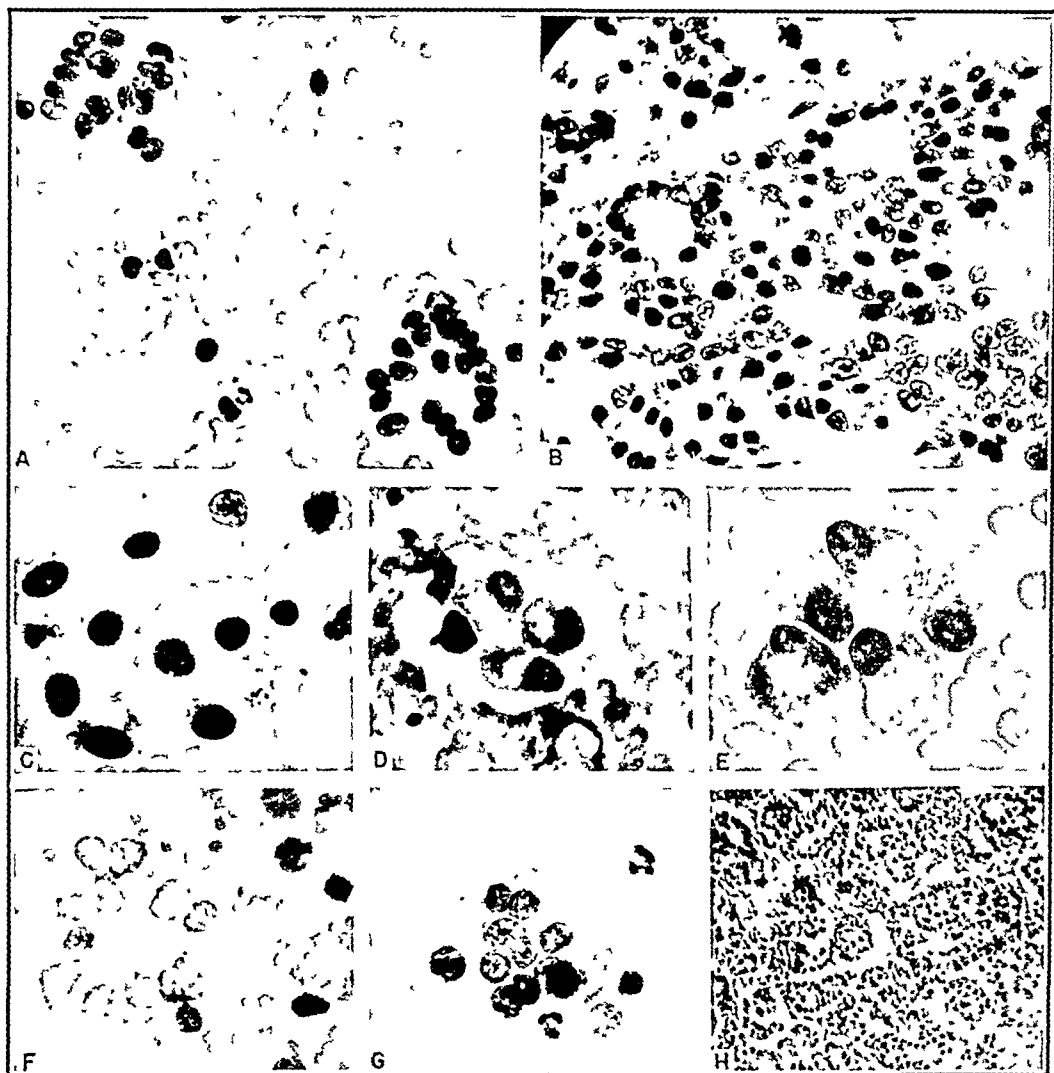


FIG. 1.—(A) W.D.W., B 93359. Aspirated sternal bone marrow (X 450). Two circular clumps of neoplastic cells are present.

(B) W.D.W., B 93359. Sectioned sternal bone marrow obtained by needle trephine from same area as A (X 450). The lightly stained tumor cells infiltrate diffusely as well as form acini.

(C.) W.D.W., B 93359. Clump of tumor cells aspirated from marrow 4 months after beginning of therapy (X 450).

(D). W.D.W., B 93359. Denser clump of tumor cells aspirated from same specimen of bone marrow as C (X 450).

(E.) E. McF., C 16069. Group of tumor cells in aspirated bone marrow 6 months after orchiectomy and beginning of estrogen therapy (X 900).

(F.) F.K., B 96216. Circular clump of tumor cells in bone marrow from sternum in patient with severe leukoerythroblastic anemia (X 450).

(G.) F.K., B 96216. Giant tumor cell aggregation aspirated from sternum 7 months after beginning of therapy.

(H.) F.M.T., B 59013. Section from interior of sternum from patient dying of hemorrhage due to thrombopenia. The marrow is largely replaced by adenocarcinoma (X 144).

Armstrong units per 100 cc. and alkaline phosphatase values of 8 and 12 units respectively. A sternal puncture was attempted and although the cortex of the bone was easily penetrated no marrow could be aspirated. A solid core of tissue was cut out with a needle trephine. A small amount of fluid marrow could then be aspirated. In the stained films the predominant normal marrow elements were segmented and non-segmented neutrophils and late normoblasts. Intermingled with these, occurring singly and in clumps, were large irregularly shaped foreign cells with 1 to 3 sharply outlined nucleoli (Fig. 1,A). Variable amounts of grayish cytoplasm were present about some of the abnormal cells. Sections of the marrow tissue removed by trephine showed infiltration by adenocarcinoma (Fig. 1,B).

A bilateral orchiectomy was performed and estrogen therapy started. During the following 2 weeks his bone pain gradually subsided. Pressure over his sternum was no longer painful. The acid phosphatase fell to 8 units per 100 cc. and the alkaline phosphatase rose to 19 units. Slight improvement in blood values with reticulocytosis and decline in the number of nucleated red blood cells was observed during his 4 weeks stay in the hospital (Table 2). The sternal puncture was repeated and infiltration with tumor cells was again observed. There was no definite change in the appearance of the neoplastic cells.

On a check-up visit 4 months later he reported steady improvement in his general health. On examination there was no tenderness of the superficial bones. The prostate gland was normal except for slight enlargement. Roentgen films of the pelvis showed conspicuous regression of the metastatic lesions. The blood values had returned to normal except for hypochromia and deformity of the red blood cells. A few immature granulocytes persisted in the circulating blood (Table 2). A third sternal puncture was done and marrow of normal cellularity and distribution of cell types was obtained. There were rare clumps of tumor cells showing greater density of nuclear chromatin and better delimited, more densely stained cytoplasm (Fig. 1, C,D).

CASE 2. L.D.W., B-96766, a 67 year old barber, was first seen at Duke Hospital on December 30, 1946. He had enjoyed good general health until 8 months previously when he became suddenly dizzy and short of breath while working. Friends called his physician and he was admitted to a local hospital for a few days of observation. After discharge he rested at home for 2 or 3 months

and then returned to work. A few weeks later he began to have recurrent pain about his shoulders and arms with physical exertion, severe enough to "cut off his breath." On one occasion when the pain lasted several hours he was admitted to his local hospital and given oxygen therapy. Three weeks before his clinic visit he began to have severe pain more or less constantly about his hips, low back and chest. Urination became frequent, painful, and the urine bloody. His legs began to swell markedly.

Physical examination showed that he was an obese, acutely ill white male. The blood pressure was 140/86 mm. of mercury. All movements of the trunk and extremities were exquisitely painful. There were no superficial tumor masses or enlarged lymph nodes. There was pronounced tenderness to light pressure over his clavicles, sternum, right humerus, costal margins and spines of the lumbar vertebrae. His heart was not definitely enlarged and the rate, rhythm and sounds were normal. The lung fields were clear. No abdominal organs or masses were palpable. There was pitting edema as high as the knees. The prostate gland was irregular in contour, hard and tender. There was diffuse neoplastic infiltration about the region of the seminal vesicles and into the pelvic tissues.

Examination of the peripheral blood showed a slight anemia with multi-segmented neutrophils and a few immature granulocytes (Table 2). The urine appeared smoky and contained a moderate amount of protein. There were innumerable red blood cells in the urinary sediment. Serologic tests for syphilis were negative. Blood chemical determinations were as follows: non-protein nitrogen 29 mg., calcium 10.0 mg., and phosphorus 1.8 mg. per 100 cc. The alkaline phosphatase was 14 King-Armstrong units per 100 cc. and the acid phosphatase 105 units. Roentgen examination of the chest, spine and pelvis showed a slight mottling and increased density of the lumbo-sacral vertebrae and iliac bones.

Bone marrow was aspirated from the sternum in a particularly tender area below the manubrium. The cortex was easily penetrable by the needle. With strong aspiration, however, only a small drop of sanguinous material could be obtained. Using the needle trephine a core of tissue was cut out and then marrow could be aspirated without difficulty. In the stained films the predominant cells were obviously foreign to the bone marrow, and occurred in sheets and circular clumps. The cells were somewhat larger than neutrophilic myelocytes. Their nuclei were large, variable in size and had a fine chromatin pattern and indistinct nucleoli. The cytoplasm

was poorly delimited at the periphery and often vacuolated. With Wright's stain the cytoplasm colored a weak blue. Bone marrow aspirated from a second puncture site a few millimeters from the first appeared to be normal in every respect.

A bilateral orchiectomy was performed on Jan. 4, 1947. Premarin was given orally in a dose of 4.75 mg. per day for 2 weeks and then 1.25 mg. per day. One week after orchiectomy the acid phosphatase had fallen to 15 units and the alkaline phosphatase to 13 units per 100 cc.

On a check-up examination 3 months later, he reported gradual improvement. He had far less pain about his legs and hips. His weight had increased excessively and he tired easily. Ankle edema developed with activity. Physical examination showed very slight tenderness over the superficial bones. The prostate gland was smaller, smoother and less indurated. The acid phosphatase had fallen to 2 units and the alkaline phosphatase had risen to 32 units per 100 cc. The blood values were all normal and there were no immature granulocytes in the circulating blood (Table 2). Re-examination of the bone marrow showed that a few tumor cells could still be identified. The nuclei of these cells were

rounder, more densely stained and the nucleoli smaller. The cytoplasm was more deeply stained and sharply delimited.

The pain and stiffness in his back and extremities gradually disappeared and in a few more weeks he was able to return to work. Physical examination 8 months after the beginning of treatment showed no relevant abnormalities. Roentgen-ray films of the chest, lumbar spine and pelvis showed no definite skeletal disease. The blood values were normal. Sternal puncture was again performed. There was no increase in bone density and with aspiration he had considerable suction pain. Fluid marrow was obtained. The total cellularity and differential cell count were normal. An occasional large foreign cell as previously encountered could still be identified.

CASE 3. H. McN., A-91961, a Carolina farmer, was 59 years old when first admitted to the Urologic Service of Duke Hospital on Sept. 20, 1942, for the treatment of kidney colic. He had had several attacks of flank pain previously and had passed 2 small stones. Mild symptoms of prostatism were elicited and examination of the prostate gland showed benign hypertrophy. An impacted calculus was found in the right ureter and



Fig. 2.—H. McN., A 91961. Roentgenogram of hip showing large area of osteolytic destruction about acetabulum and position of needle when aspirating tumor implants.

this was removed by ureterolithotomy. His recovery was uneventful.

During the next 5 years the symptoms of bladder neck obstruction gradually increased and finally he developed acute urinary retention. After a few days of intermittent catheterization at home he was again admitted to the hospital on Sept. 23, 1947. His general physical examination showed no relevant abnormalities. Two urologic consultants believed that his prostate gland showed only benign hypertrophy while one questioned the presence of a carcinomatous nodule. A suprapubic prostatectomy was performed. Pathologic examination of the resected specimen was reported to show benign glandular hyperplasia. Convalescence was prolonged due to pulmonary infarction but was eventually satisfactory.

Ten months after the prostatectomy he developed pain in his left hip and knee. This gradually increased during the 2 or 3 months before he again sought advice. On examination he walked with a limp. There was pain and limitation of motion about the left hip. Rectal examination showed post operative induration of the prostate gland. Roentgenograms of the pelvis showed a large area of bone destruction about the left hip joint (Fig. 2). The acid phosphatase was 2 King-Armstrong units and the alkaline phosphatase 7 King-Armstrong units per 100 cc.

Hematologic studies were requested. The peripheral blood and sternal bone marrow were found to be entirely normal. Bone marrow aspirated from the left iliac crest was of average cellularity and distribution of cell types. No foreign cells were seen. A needle was then implanted into the edge of the destructive lesion surrounding the acetabulum (Fig. 2). Films made from the aspirated marrow contained clumps of neoplastic tissue resembling adenocarcinoma implants. After this discovery was made, the sections of the resected prostate gland were reviewed and areas containing carcinoma were found. An orchiectomy was done and estrogen therapy was started. There was immediate relief of pain about the left hip.

**Summary of Findings.** The preceding cases illustrate typical features of the natural history of carcinoma of the prostate gland, some problems in diagnosis, and the results of present day therapy<sup>1,6,7,10,12,13</sup>. The major findings in the entire group of 30 patients are summarized in Table 1. While the commonest symptoms resulted from

Table 1.—SUMMARY OF FINDINGS IN 30 PATIENTS WITH CARCINOMA OF THE PROSTATE.

|  | No. of Cases |
|--|--------------|
| <i>Presenting Symptoms:</i>  |              |
| Bladder neck obstruction   | 20           |
| Skeletal pain  | 18           |
| Altered or abnormal bowel habit  | 11           |
| Weakness with anemia   | 7            |
| Bleeding and purpura   | 1            |
| <i>Interpretation of gland by palpation:</i>   |              |
| Carcinomatous induration   | 25           |
| Probable carcinoma   | 2            |
| Not carcinoma  | 3            |
| <i>Pronounced tenderness of sternum</i>  | 14           |
| <i>Roentgen-ray and Chemical findings:</i>   |              |
| Osteoblastic skeletal lesions  | 15           |
| Acid phosphatase above 3 K-A units   | 17           |
| Alkaline phosphatase above 10 K-A units  | 17           |
| <i>Hematologic findings:</i>   |              |
| Hemoglobin less than 12 gm. per 100 cc.  | 17           |
| Tumor cells demonstrated in marrow   | 17           |
| Leukoerythroblastic anemia   | 8            |
| <i>Number with osteoblastic skeletal lesions and, or, pathologically verified metastases</i> | 21           |

bladder neck obstruction, skeletal pain from tumor metastases was nearly as frequent. An altered bowel habit suggested the possibility of colonic neoplasm in 11 patients. Symptoms due to anemia or bleeding occurred in 8.

Rectal examinations as recorded by a group of urologic consultants showed diffuse or nodular induration in 25 cases. One gland in 6 was considered by palpation to be normal or questionably abnormal.

Pronounced tenderness of the superficial bones, particularly the sternum, elicited by pressing firmly on the periosteum, was a significant and useful physical sign present in 14 patients<sup>3</sup>. Tumor cells were demonstrated in the bone marrow of 12 of these and impenetrable bone rendered sclerotic by metastases in another<sup>11</sup>. In one instance sternal marrow metastases were demonstrated without bone tenderness, anemia, Roentgen abnormality,

TABLE 2.--EFFECT OF CASTRATION AND ESTROGEN THERAPY ON LEUKOERYTHROBLASTIC ANEMIA DUE TO METASTATIC CARCINOMA OF THE PROSTATE

| Date                      | Hb.<br>(gm. per<br>100 cc.) | RBC<br>(mill.per<br>cmm.) | WBC<br>(per<br>cmm.)  | Hemato-<br>crit | Reticu-<br>locytes<br>% | Differential leukocyte counts:                        |      |                         |                |        |     |     | Nuc.RBC/<br>100 WBC |       |
|---------------------------|-----------------------------|---------------------------|---|-----------------|-------------------------|---|------|-------------------------|----------------|--------|-----|-----|---------------------|-------|
|                           |                             |                           |   |                 |                         | Seg.  | Band | Meta-<br>myelo-<br>cyte | Myelo-<br>cyte | Lymph. | Eo. | B.  |                     | Mono. |
| Case 1, W. D. W., B 93359 |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 12/4/46                   | 5.1                         | 2.23                      | 9360  | 18.0            | 4.5                     | 34  | 19   | 8                       | 1              | 29     |     | 1   | 8                   | 29    |
|                           | <u>Sternal Marrow:</u>      |                           | Tumor cells, clumped and singly. Sections: adenocarcinoma.      |                 |                         | (Therapy: 500 cc. transfusion; orchectomy; estrogens) |      |                         |                |        |     |     |                     |       |
| 12/18                     | 6.0                         | 2.57                      | 7800  | 19.0            | 3.5                     | 56  | 16   |                         |                | 23     |     |     | 5                   | 29    |
| 12/24                     | 5.5                         | 2.1                       | 7600  | 19.0            | 7.5                     |   |      |                         |                |        |     |     |                     |       |
| 12/31                     | 6.4                         | 2.16                      | 7700  | 23.0            | 9.0                     | 50  | 11   | 6                       |                | 27     | 1   | 1   | 4                   | 4     |
|                           | <u>Sternal Marrow:</u>      |                           | Tumor cells present as before. No definite change.              |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 4/23/47                   | 11.0                        | 5.06                      | 5650  | 39.5            | 2.0                     | 59  |      | 2                       |                | 36     |     |     | 3                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Normal cellular marrow. Scattered clumps of altered tumor cells |                 |                         |   |      |                         |                |        |     |     |                     |       |
| Case 2, L. D. W., B 96766 |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 12/31/46                  | 11.7                        | 4.31                      | 8250  | 39.2            | 1.0                     | 64  |      | 1                       | 1              | 26     |     | 2   |                     | 6     |
|                           | <u>Sternal Marrow:</u>      |                           | Clumps and sheets of tumor cells.                               |                 |                         | (Therapy: 1/4/47 orchectomy; estrogens)               |      |                         |                |        |     |     |                     |       |
| 3/11/47                   | 13.5                        | 4.65                      | 6350  | 43.0            |                         | 61  |      |                         |                | 27     | 2   | 2   | 8                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Normal Cellular marrow. Rare foreign cell.                      |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 9/10                      | 15.2                        | 4.99                      | 7500  | 45.0            |                         | 62  |      |                         |                | 28     | 5   |     | 5                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Normal cellular marrow. Rare altered tumor cell.                |                 |                         |   |      |                         |                |        |     |     |                     |       |
| Case 3, T. L. M., B 90555 |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 10/10/46                  | 10.4                        | 3.5                       | 7550  | 33              | 1.0                     | 46  | 9    | 2                       |                | 36     | 1   |     | 6                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Tumor cells, clumped and singly. Trepine: carcinoma.            |                 |                         | (Therapy: orchectomy; estrogens)                      |      |                         |                |        |     |     |                     |       |
| 10/18                     |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 9/23/47                   | 12.9                        | 4.72                      | 10,250  | 43              | 0.7                     | 56  | 3    |                         |                | 32     | 3   | 1   | 5                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Bone impenetrable.  |                 |                         |   |      |                         |                |        |     |     |                     |       |
| Case 4, F. H. K., B 96216 |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 10/24/47                  | 4.7                         | 2.0                       | 6850  | 16              | 6.0                     | 30  | 39   | 1                       |                | 15     | 2   | 2   | 11                  | 2     |
| 10/27                     | <u>Sternal Marrow:</u>      |                           | Replacement with sheets and clumps of tumor cells.              |                 |                         | (Therapy: orchectomy, estrogens, transfusions)        |      |                         |                |        |     |     |                     |       |
| 11/4                      | 5.3                         | 1.98                      | 6350  | 17              |                         | 36  | 35   |                         |                | 16     | 1   | 2   | 9                   | 1     |
| 5/27/48                   | 12.8                        | 4.0                       | 9150  | 37              | 3.2                     | 72  | 2    |                         |                | 11     | 2   | 2   | 6                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Normal marrow. Very rare tumor cell clump.                      |                 |                         |   |      |                         |                |        |     |     |                     |       |
| Case 5, E. P., C 32731    |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 4/15/48                   | 6.0                         | 2.37                      | 5560  | 21              | 3.4                     | 68  | 8    | 1                       |                | 19     |     | 0.5 | 3                   | 0.5   |
| 4/30                      |                             |                           |   |                 |                         | (Therapy: orchectomy; estrogens)                      |      |                         |                |        |     |     |                     |       |
| 8/5                       | 8.5                         | 3.0                       | 6550  | 27              | 1.5                     | 64  | 2    |                         |                | 23     |     | 1   | 10                  |       |
|                           | <u>Sternal Marrow:</u>      |                           | Crowded with tumor cells showing early effect of treatment.     |                 |                         |   |      |                         |                |        |     |     |                     |       |
| Case 6, E. McF., C 16069  |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 11/28/47                  |                             |                           |   |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 12/2                      | 10.8                        | 3.75                      | 8900  | 31              | 3.1                     | 81  | 2    |                         |                | 12     |     | 1   | 5                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Normal cellular marrow. Rare tumor cells                        |                 |                         | (Therapy: orchectomy; estrogens)                      |      |                         |                |        |     |     |                     |       |
| 5/25/48                   | 9.2                         | 3.4                       | 8150  | 29.5            | 3.4                     | 54  | 18   |                         |                | 23     |     | 1   | 4                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Infiltration with clumps and sheets of foreign cells.           |                 |                         | (Stilbestrol increased to 5 mg. daily)                |      |                         |                |        |     |     |                     |       |
| 8/10                      | 9.5                         | 3.2                       | 8200  | 28              | 1.3                     | 52  | 8    |                         |                | 31     | 3   |     | 6                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Thorough infiltration with altered tumor cells.                 |                 |                         |   |      |                         |                |        |     |     |                     |       |
| 11/26                     | 7.8                         | 2.6                       | 4500  | 23              |                         | 73  | 3    | 3                       |                | 14     | 2   |     | 5                   |       |
|                           | <u>Sternal Marrow:</u>      |                           | Replacement with tumor cells in clumps and singly.              |                 |                         |   |      |                         |                |        |     |     |                     |       |



or elevated phosphatase activity being present.

An acid phosphatase level above 3 King-Armstrong units per 100 cc. was found in 17 of the 30 patients. Four with normal values were demonstrated to have tumor implants in the bone marrow.

The hemoglobin was less than 12 gm. per 100 cc. in 17 of the 30 patients. Tumor metastases were present in 16 of these individuals. The blood urea nitrogen was elevated in the 17th. Bone marrow metastases were demonstrated in 4 individuals who were not anemic.

The more severe grades of anemia were of the so-called leukoerythroblastic type with immature granulocytes or nucleated red cells present in the circulating blood<sup>34</sup>. The latter abnormalities were not prominent unless the hemoglobin was reduced to 7.5 gm. or less. Leukocytosis was not observed. The effect of castration and estrogen therapy was studied in 6 patients with leukoerythroblastic anemia in whom marrow metastases were demonstrated (Table 2). In the 5 patients whose general response was good the anemia became less severe or disappeared in a few weeks. As the anemia regressed the amount of tumor in the marrow demonstrable by serial aspirations decreased likewise (Table 2). Bony sclerosis severe enough to make it impossible to penetrate the sternum or other bones with a needle developed in one patient who had no anemia at the time or evidence of extra-medullary blood formation. In the 6th patient the clinical response to castration and estrogen therapy was poor. There was progressive increase in the Roentgen evidence of skeletal metastases and in bone pain and tenderness. The blood values continued to fall and the amount of tumor tissue demonstrable by marrow aspiration increased.

The features by which tumor cells in bone marrow preparations may be reliably identified have been discussed at length by many investigators<sup>5,8,9,16,17,21,22,26,35</sup>. Photographs of typical implants from prostatic carcinoma are reproduced in Figure 1. The most notable characteristic of tumor cells in bone marrow is that they are foreign cells, unlike those normally present or any derived from the marrow in different pathologic states. A second feature is that tumor cells tend to adhere together in small or large clumps in narrow films in which the other cells are well spread. They are sometimes arranged in circles suggestive of sectioned acini (Fig. 1, A. F.). The individual cells may vary moderately in size. The chromatin pattern of their nuclei is usually quite dense and fine, but may be coarsely reticular. Nucleoli are frequently large and prominent or multiple. The cytoplasm, often torn away during the preparation of spread films, is usually abundant but cell boundaries are poorly delimited. With Wright's stain the cytoplasm colors greyish-blue and may contain fine granules. Considerable variation in the morphology of tumor cells that metastasize from prostatic carcinoma occurs, however, from patient to patient.

Two or 3 months after orchectomy and the initiation of estrogen therapy the quantity of neoplastic tissue demonstrable in aspirated bone marrow is usually greatly reduced. Tumor cells may be difficult to demonstrate even by repeated punctures in areas that once contained abundant foreign tissue. The neoplastic cells that remain occur in smaller, more compact clumps containing 2 to 5 cells with more densely stained and better delimited cytoplasm. Giant cells may develop (Fig. 1, G.). The nuclei are usually more eccentric and pyknotic and their

nucleoli less prominent than before therapy.

**Discussion.** Somewhat over 60% of patients diagnosed as having prostatic carcinoma have clinical evidence of bony metastases. Several routes of tumor spread have been postulated: direct extension of the primary growth, direct and retrograde migration by lymph channels, hematogenous dissemination, and others. The frequency with which metastatic implants can be demonstrated in tissue as remote as the sternal marrow, and the predominant localization of the metastases in the well-vascularized bones containing red marrow, suggests that blood stream dissemination is the important route of spread of this neoplasm. Tumor cells are occasionally discovered by marrow study before anemia, structural weakening of the skeleton, or roentgenologic abnormalities have developed<sup>26</sup>. Implantation and growth of tumor occurs thus primarily in the hemopoietic rather than in the osseous tissues.

Metastases of prostatic carcinoma have been detected clinically in the past chiefly by the roentgenologic demonstration of the characteristic destructive and proliferative bony lesions. Other findings almost equally indicative of tumor metastases are increased phosphatase activity, pronounced bone tenderness and anemia in the absence of azotemia. When one or more of these abnormalities are present, tumor cells can be aspirated from the bone marrow in a high percentage of cases.

Since carcinoma of the prostate is one of the few tumors amenable to chemotherapy, recognition of this gland as the source of metastases in obscure cases is highly important. The correct diagnosis is particularly likely to be missed when there is no palpable abnormality in the gland itself, when only localized bone lesions are pre-

sent, or when the roentgenologic findings are atypical in other respects. In the latter instances marrow aspirations from areas particularly involved may yield valuable diagnostic findings<sup>23,33</sup>.

The mechanism by which malignant tumors in general lead to anemia has been a matter of much discussion<sup>4,17,18,27,28,34</sup>. External bleeding, impaired nutrition, tissue necrosis, and fever are common in many neoplastic processes. Accelerated blood destruction has been observed rarely. None of these factors has been especially prominent in patients with carcinoma of the prostate. In many different tumors infiltration of the bone marrow occurs. This may interfere with the function of the hemopoietic tissues by marrow replacement, by producing fibrosis and scarring, perhaps secondary to disturbances in vascular supply as by arterial emboli, and the like. Many observers have failed to find a general correlation between the volume of bone marrow replaced by tumor and the severity of the anemia in neoplasms. Marrow fibrosis has sometimes been prominent with little tumor being present<sup>34</sup>. Piney<sup>20</sup> described a gelatinous transformation of marrow in some patients with tumor implants in the bone marrow similar to the changes produced by Huggins and Wiege<sup>11</sup> by disruption of the nutrient arteries.

Three patients with myelophthisic anemia occurring as the presenting manifestation of prostatic carcinoma with skeletal metastases were reported recently by Commons and Strauss<sup>2</sup>. In agreement with others, they noted improvement in the anemia after castration and stilbesterol therapy. They did not record bone marrow examinations and they regarded the mechanism of the anemia as somewhat obscure. They thought it reasonable to believe, however, that the hemopoietic marrow was crowded out by abnormal tissue. The findings in the present study

confirm this suggestion. In our series the individuals with carcinoma of the prostate gland who were anemic almost invariably had bone metastases. In those with only localized or scanty diffuse implantation, however, the peripheral blood was normal. When anemia was present its severity paralleled the degree of marrow infiltration. In those with heavy infiltration or with marrow replacement the anemia improved after therapy as the quantity of neoplastic tissue regressed, or became more severe as tumor growth proceeded in spite of therapy. The hematologic response of individuals with anemia due to marrow invasion by prostatic cancer has been of prognostic value reflecting the overall therapeutic response to endocrine therapy<sup>10,12,13</sup> and should be more generally utilized.

**Summary.** Tumor cells were demonstrated by aspiration in the sternal or iliac bone marrow in 17 of 30 patients with carcinoma of the prostate gland. Twenty-one had Roentgen-ray or pathologic evidence of metastases. Implantation appears to occur primarily in the hemopoietic rather than in the osseous tissues. Anemia in the absence of azotemia occurred only in those who had metastases. Gross infiltration of the bone marrow was associated with severe anemia. Immature granulocytes and nucleated red blood cells became prominent in the circulating blood when the hemoglobin was reduced to 7.5 gm. or below. Following castration and estrogen therapy, the anemia regressed as the amount of tumor tissue demonstrable in the bone marrow decreased, or became more severe as tumor growth progressed in spite of therapy.

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# THE PITUITARY GLAND OF RATS WITH EXPERIMENTAL GOITER\*

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INTERDEPENDENT relationships between the various endocrine organs have long been identified and experimentally tested. Hormones elaborated by a given endocrine gland stimulate a cytologic response in another and the extirpation of one is likely to incite cytologic and functional disturbances in another. The pituitary-thyroid interrelationship has been thoroughly demonstrated clinically and extensively investigated experimentally. Thyrotropic hormone when given to normal animals incites a thyroid hyperplasia, with consequent elaboration of thyroid hormone. Conversely, thyroidectomy, which results in lowered concentrations of thyroxin in the blood, exerts a stimulating effect upon certain constituents of the anterior lobe of the pituitary gland and a thyroid-stimulating hormone is elaborated.

The rather recent identification and development of a number of goitrogenic substances have provided a new approach to a study of the pituitary-thyroid axis. Seeds of the Brassica plant family, soybean flour, phenylthiocarbamide, certain sulfonamide compounds, thiourea-like drugs, 4,2'-diaminophenyl-5'-thiazolyl sulfone (promizol) and many other drugs have been shown to be goitrogenic.

Most of these goitrogens induce a functional thyrostatics, wherein the thyroid cell collects reduced amounts

of iodine, thereby greatly restricting the amounts of thyroxin that the thyroid cell may synthesize. Concentrations of thyroxin in the blood are consequently lowered, with the result that presumably increased amounts of thyrotropic hormone released by the anterior lobe of the pituitary stimulate a marked hyperplasia of the thyroid which results in the development of large goiters, some of which have been reported. These thyroid changes may be prevented, even while a goitrogen is being administered, by providing the daily requirements of thyroxin (Griesbach and Purves 1945<sup>11</sup>; Higgins and Joneson 1946<sup>15</sup>). Likewise, goiters do not develop in animals given the goitrogen, if they were previously hypophysectomized (Griesbach, Kennedy and Purves 1941<sup>12</sup>; Higgins and Ingle 1946<sup>14</sup>). Coincident with the development of the goiter, prolonged administration of the goitrogen has been shown to produce marked degrees of exophthalmos. Since it has been shown that protrusion of the eyes may be produced in guinea pigs by giving a thyroid-stimulating hormone<sup>6</sup>, there is at least some reason to believe that the symptoms affecting the eyes which ensue on the use of certain goitrogens, are due to increased elaboration of thyroid-stimulating hormone.

Thus the experimental data implicate the pituitary gland in inciting the thy-

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roid hyperplasia, but observations with respect to the cytologic changes within the anterior lobe of the pituitary gland of animals given goitrogens are somewhat conflicting.

Marine, Rosen and Spark<sup>18</sup> (1935) described an increase in the size of the cells and a decrease of the acidophilic granules of the pituitaries of rabbits fed a goitrogenic diet. Nelson and Warkany<sup>21</sup> (1938) fed rats a rachitogenic diet which was shown to be goitrogenic, and described groups of large pale cells in the pituitary gland which gave it a spongy appearance. Sharpless and Hopson<sup>23</sup> (1940) by use of a soybean diet, showed decreased proportions of acidophilic cells, and increased proportions of basophilic cells. Griesbach<sup>9</sup> (1941) described conspicuous cell changes in the pituitary gland of animals fed a diet of *Brassica* seeds. These included a rapid increase in the number of basophilic cells with vacuolations. Griesbach and Purves<sup>10</sup> (1943) found a very marked increase in the percentage of basophils within the anterior lobe of the pituitaries of those animals fed their rape seed diet. This seemed to be correlated with corresponding increases in the thyrotropic activity of the serum. Williams, Weinglass, Bissell and Peters<sup>24</sup> (1944), however, reported that the pituitary glands of thiouracil-treated animals were smaller than normal and that microscopic changes, incident to giving the goitrogen, could not be detected. Griesbach and Purves<sup>11</sup> (1945) examined the cytologic response of the pituitary to known degrees of thyroxin deficiency and concluded that a slight reduction in the concentration of thyroxin in the serum caused an increase in the percentages of basophils and that the basophilic cells of the anterior lobe were the source of thyrotropic secretions.

Mellgren<sup>19</sup> (1945) reported an increase in the number of hyaline basophils and hypertrophic amphophils in

the pituitary glands of patients with Cushing's disease or adrenal virilism; which increase he considered to be an expression of a corticotropic hyperfunction of the anterior pituitary. In a recent report, Mellgren<sup>20</sup> (1948) concluded from an extensive study on normal and hypophysectomized rats that the pituitary changes he had described in the adrenogenital diseases were not the result of a hyperfunction of the adrenal cortex. The adrenal changes, he believed, were the results of the increased production of corticotropic hormone which produced the hyperfunction of the adrenal cortex.

Changes in the pituitary incited by lowered concentrations of thyroxin induced by giving certain goitrogens are similar in many respects to those which ensue on thyroidectomy. Zeckwer, Davison, Keller and Livingood<sup>26</sup> (1935) described a depletion of the acidophils and an increase in the number of basistaining cells. Numbers of "thyroidectomy cells" were taken to be transformed from cells containing blue granules.

The present report includes the results of a study wherein we have examined the pituitary glands of groups of animals which were given 3 different goitrogens for periods up to 90 days.

**Experimental Methods.** Vigorous male rats, weighing 60 to 90 gm., were selected and isolated for this study. They were housed in metal cages, on metal screen, and fed the standard laboratory ration used at the Institute of Experimental Medicine. Both food and water were provided as desired. Four groups of animals were arranged: 3 of these groups received the 3 goitrogens selected for study, and the 4th group served as controls. The goitrogens selected for study of the changes induced within the pituitaries were promizol, diethyl thiobarbituric acid (thiobarbital) and 2-mercapto 4-pyrimidone (thiouracil). We used the tables provided by the extensive study of McGinty and Bywater<sup>16,17</sup> (1945), which was based on the ability of the drug to reduce the iodine content of the thyroid to 12 mg.%, to establish the fol-

lowing concentrations of these goitrogens in the diet provided the test animals. Promizol was given in amounts equivalent to 0.30% of the diet; thiobarbital, equivalent to 0.44% of the diet, and thiouracil, 0.54% of the diet.

Observations were made on the basal metabolic rates, the thyroid and the pituitary glands at the end of 24, 48 and 72 hours and of 7, 14, 30, and 90 days of experimental restriction. The apparatus employed for the computation of the basal metabolic rates has been previously described (Chapman, Baldes and Higgins<sup>2</sup>, 1944). All animals were killed by deep ether anesthesia. The thyroid glands were removed, weighed immediately on a Roller-Smith torsion balance, fixed in 10% formalin and appropriately stained. Acinar cell heights were measured by means of a Leitz echelon ocular micrometer. The pituitary glands were removed, weighed on the torsion balance and fixed in Regaud's fluid, consisting of 80 cc. of a 3% solution of potassium dichromate in 20 cc. of full-strength formaldehyde.

After fixation for 8 days, with frequent change of fixative, the glands were washed, dehydrated and transferred to cedar oil, embedded and cut in serial sections 3 microns in thickness. After rehydration, the sections were mordanted in a 3% solution of potassium dichromate and stained according to a modification of the Cleveland-Wolfe<sup>3</sup> (1932) staining technic.\* In sections appropriately stained, the erythrocytes stain light yellow, connective tissues stain blue and the large glandular cells with nongranular cytoplasm remain unstained or stain very light blue; other granular cells stain dark blue, with a variable amount of purplish red granules and still others may contain large yellowish orange granules.

An adaptation of the method of Rasmussen and Herrick<sup>22</sup> (1922) for determining the percentage distribution of the cells comprising the anterior lobe was used. By this method a section from each quadrant of the gland was used; all the cells were counted in every fifth oil-immersion field in every fifth row. In this way it is possible to avoid counting a cell more than once.

**Results. Basal Metabolic Rates.** Basal metabolic rates obtained at frequent intervals during the 90-day test period show that hypothyroidism had been produced in all animals. At the end of the test period the average

number of calories per sq. m. per hour consumed by animals comprising the control group was 46.1. In animals receiving promizol, the figure was 30.4 calories; in those receiving thiobarbital, it was 34.3, and in those receiving thiouracil it was 38 calories per sq. m. per hour. Thus promizol had apparently induced the greatest decline in oxygen consumption, resulting in a basal rate of minus 34%; thiobarbital a minus 25.6%, and thiouracil a minus 17.6%. The mean basal rate of those animals which had been previously thyroidectomized, and given the standard ration without goitrogen, was a minus 16.1%.

**Thyroid Glands.** Gross changes in the appearance of the thyroid glands were first detected at the end of the 72-hour test period. Glands of test animals were more hyperemic than those of the controls and significant increases in the weight of the thyroid gland of each test animal were recorded. On the seventh day the glands of all test animals weighed approximately twice that of the controls; on the ninetieth day the relative weights of the thyroid glands of animals taking promizol were 12 times those of their controls, those taking thiobarbital were 5 times those of their controls, and those taking thiouracil, in the amounts given, were approximately 4 times those of their controls.

Histologic changes accompanied the changes in weight of the gland, and, in this experiment, were essentially those which have been described in earlier reports regarding reactions of thyroid glands to goitrogens. Loss of acinar colloid was an early indication of change in all thyroids examined. Coincident with colloid fragmentation were the increases in acinar cell heights, resulting in highly columnar

\* We are indebted to Dr. J. F. Hartmann of the Department of Anatomy of the University of Minnesota for his personal direction in the use of his own modification of the staining procedure employed in this study.

epithelium. In the longer periods, papillary infoldings of the epithelium which resembled the parenchymatous hyperplasia of clinical exophthalmic goiter, were produced. New acini appeared as a result of clefts in acinar epithelium of older acini.

Significant increases in the height of the acinar cell epithelium were recorded as early as 72 hours after the beginning of experimental restriction. At this time the mean acinar cell height of thyroid glands of the control animals was 3.58 microns; that of animals taking promizol was 10.60 microns, that of those taking thiobarbital was 7.89 microns and that of those taking thiouracil was 8.28 microns. At the end of the 30-day test period, corresponding figures for these respective groups

glands of the test animals were certainly more hyperemic.

The absolute weights of the glands were not significantly altered among the groups of animals by the conditions of the experiment. At 72 hours, for example, the average weight of the glands of 5 control animals, weighing 63.6 gm. was 2.7 mg.; the weight of glands of animals taking promizol was 3 mg.; of animals taking thiouracil was 3.6 mg. and of animals taking thiobarbital it was also 3.6 mg. The average body weight of animals in the test groups at this time was slightly greater than that of animals in the control group; when the relative weights of the glands were contrasted, differences were not apparent (Table 1).

The data assembled on the fourteenth

TABLE 1. WEIGHTS OF PITUITARY GLANDS OF RATS RECEIVING GOITROGENS

| Elapsed time | Control         |                             | Promizol-fed     |                             | Thiouracil-fed   |                             | Thiobarbital-fed |                             |
|--------------|-----------------|-----------------------------|------------------|-----------------------------|------------------|-----------------------------|------------------|-----------------------------|
|              | Body weight, gm | Pituitary gland weight, mg. | Body weight, gm. | Pituitary gland weight, mg. | Body weight, gm. | Pituitary gland weight, mg. | Body weight, gm  | Pituitary gland weight, mg. |
| 72 hours     | 63.6            | 4.3 $\pm$ 0.1               | 72.0             | 4.2 $\pm$ 0.1               | 78.0             | 4.6 $\pm$ 0.1               | 75.2             | 4.8 $\pm$ 0.3               |
| 14 days      | 121.6           | 4.6 $\pm$ 0.1               | 102.0            | 5.6 $\pm$ 0.1               | 117.2            | 5.8 $\pm$ 0.1               | 143.0            | 5.5 $\pm$ 0.2               |
| 30 days      | 162.5           | 3.8 $\pm$ 0.2               | 105.2            | 5.5 $\pm$ 0.1               | 126.5            | 5.3 $\pm$ 0.1               | 105.5            | 6.8 $\pm$ 0.3               |
| 90 days      | 264.0           | 3.8 $\pm$ 0.1               | 205.5            | 6.5 $\pm$ 0.2               | 181.6            | 5.9 $\pm$ 0.1               | 162.8            | 6.8 $\pm$ 0.3               |

were 3.68, 11.04, 10.31 and 10.28 microns. At the termination of the experiment (90 days) such marked stimulation of the thyroid epithelium had occurred in all groups, and such extreme patterns had resulted, that attempts to gain any accurate measurements of the height of the columnar cells were not made.

*Pituitary Glands.* Certain of the data on the relative weights of the pituitary glands assembled from animals killed at various intervals during the 90-day test period have been condensed in Table 1. Grossly, the pituitaries of the test animals did not appear to differ greatly from those of the control group; although, as the experiment progressed, it was obvious that the

day of the experiment indicate that there were some real increases encountered in the absolute weights as well as in the relative weights of the glands. At this time the mean absolute weights of the glands of the 4 groups were: controls, 4.6 mg.; promizol-fed, 4.7 mg.; thiouracil-fed, 6.2 mg.; and thiobarbital-fed, 7.8 mg. The relative weights—weight of pituitary gland per 100 gm of body weight—showed slight but significant increases (Table 1).

At the termination of the experiment, pituitary glands of all test animals were extremely hyperemic; yet only slight increases in the weights of glands of control animals were recorded for the glands of test animals. The average weight of the glands of the control

animals at the termination was 10 mg.; of promizol-fed animals, 13.3 mg.; of thiouracil-fed, 10.7.; and of thiobarbital-fed, 11.1 mg. The relative weights of the pituitaries, however, were all significantly higher in test animals than in controls. All test animals had gained less in body weight than those of the control group; so that, per 100 gm., the weights of the pituitaries were greatly increased (Table 1).

Although the absolute average weights of the pituitary glands of these test animals were not greatly altered from the average weight recorded for the controls, yet, with the technic employed, microscopic changes were evident as early as 72 hours after experimental restriction was started. The percentage distribution of the cell populations of the pituitary glands of control

and test animals studied at 24 and 72 hours and 7 days, and at 14, 30 and 90 days of experimental restriction are graphically portrayed in Figs. 1 and 2.

Using the described technic of tabulating, we attempted to record the percentage of the 3 types of cells comprising the anterior lobes. In our hands the percentage of the acidophils of control animals varied from 54.7 (animals killed at 24 hours) to 71.3 (animals killed at 90 days). Thus the older the animal, the higher the percentage of acidophils. The percentage of basophils varied from 17.2 (animals killed at 90 days) to 34.1 (animals killed at 7 days). In contrast to the percentage of acidophils the percentage of basophils was highest in younger animals, and lowest in the older animals.

Very definite changes in the percent-

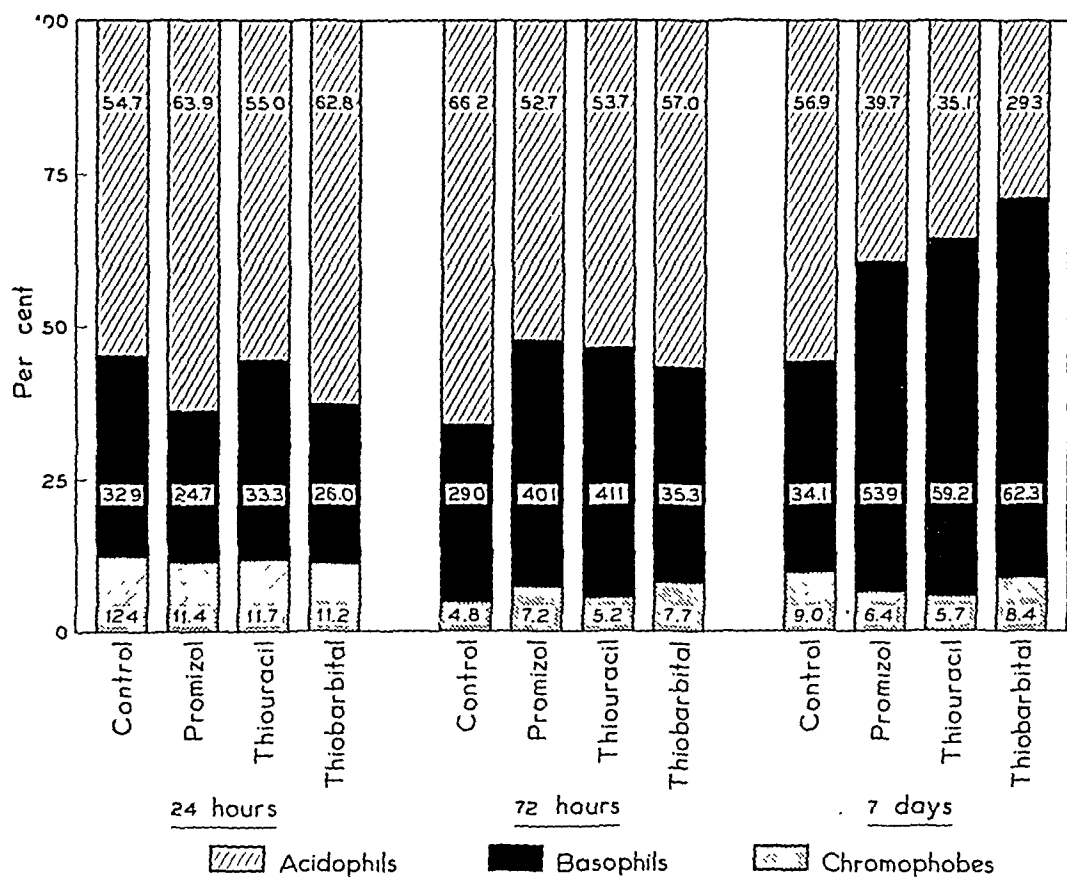


FIG. 1. The percentage distribution of cells comprising the anterior lobes of pituitary glands of animals taking the various goitrogens for 24 hours, 72 hours, and 7 days.



age distribution of the chromophil cells occurred in the anterior lobe of all animals receiving the goitrogens. In animals receiving promizol, for example, 63.9% of all cells studied at the 24-hour interval were acidophilic; 24.7% were basophilic and 11.4% were classed as chromophobes. These figures are presumably within the normal range. At the 72-hour interval 52.7% of acido-

percentage of basophils continued to rise until at the end of the experiment (90 days) only 9.8% of all cells counted were acidophils, and 82.4% were basophils.

We could not detect significant differences between the cytologic pattern of the pituitaries within the 3 groups of animals given the 3 goitrogens. In all 3 test groups extreme basophilia had

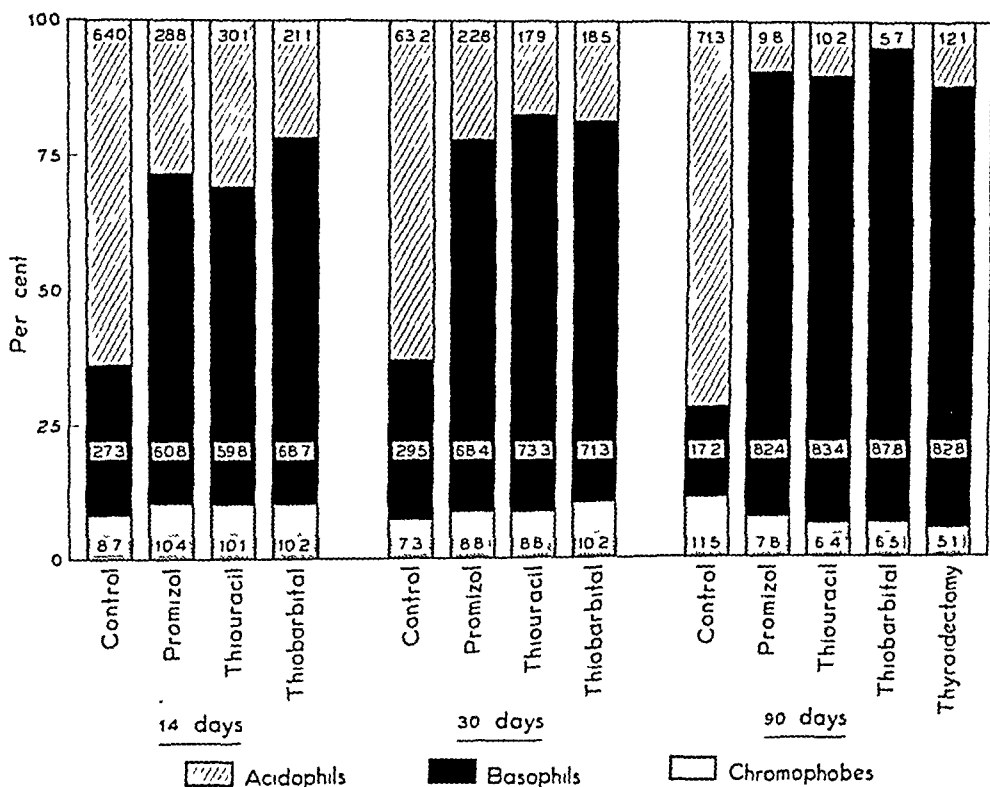


FIG. 2. The percentage distribution of cells comprising the anterior lobes of pituitary glands of animals taking the various goitrogens for 14, 30, and 90 days.

phils and 40.1% of basophils were recorded. The percentage of acidophils might still have been within the normal range, but the elevated percentage of basophils was indicative of extreme basophilia which later developed in the anterior lobes of animals taking any of the goitrogens. During the succeeding weeks of the test the percentage of acidophils continued to decline and the

developed in the anterior lobes of all animals examined. A corresponding basophilia had developed in the anterior lobes of animals which had been thyroidectomized several weeks before the experiment was started (Fig. 2.). These data show that in this latter group the percentages of acidophils, basophils and chromophobe cells were closely similar to those we obtained

for the same categories of cells in animals receiving the goitrogens we provided.

These changes in the cellular distributions within the pituitary glands of animals receiving the goitrogens were reversible. To test this, a series of animals was given the goitrogens for 30 days. At this time, from our previous data, we had reason to believe that advanced basophilia had already developed in the anterior lobes of their pituitaries. Our previous census of cells at 30 days (Fig. 2) had shown that the percentage of acidophils ranged from 17.9 to 22.8, and that of basophils ranged from 68.4 to 73.3. At the end of the 30-day period, therefore, all goitrogens were removed and all animals were fed the standard ration for an additional 30 days. All were then killed; the pituitary glands were fixed and prepared for study in the same manner as before, and the percentage distributions of the 3 types of cells were recorded. The data show that complete restoration of so-called normal percentages had not yet occurred. The percentage of acidophilic cells in these animals ranged from 54.9 to 57.2; and the percentage of basophils ranged from 36.8 to 40.0. These basophil percentages are still considerably higher than those which we had accepted as representative of normal in unstimulated pituitary glands (ranging from 17.2 to 34.1%); so that a complete return to normal distributions was not attained within the 30-day period, although marked reversible changes had certainly taken place.

**Comment.** All data assembled on the percentage distribution of cells comprising the anterior lobes of the pituitaries of all animals receiving the 3 goitrogens showed clearly that a marked basophilia had developed during the 90-day test period. Basophilia, we believe, was due to a lowered concentration of thyroxin in the blood, the

result of the inhibiting effect of the goitrogens upon thyroxin synthesis, and it represents an effort on the part of the anterior lobe of the pituitary to provide increasing amounts of thyroid-stimulating hormone. We have not assayed these glands for the content of thyroid-stimulating hormone, nor have we examined the blood serum for hormone content. Gordon, Goldsmith and Charipper<sup>7</sup> (1945) concluded that the hormone level was lower in both pituitary glands and serums of animals made goitrous by thiourea. Griesbach and Purves<sup>11</sup> (1945), on the other hand, showed that in cases of gross deficiency of thyroxin, an excess of thyrotropin was detected in the blood serum. These authors examined the cytologic and functional responses of the pituitary to various degrees of thyroxin deficiency induced by total thyroidectomy, subtotal thyroidectomy, and by combining these procedures with the administration of thiourea. They concluded that even slight reductions in the normal concentrations of thyroxin induced increased activity and increased numbers of basophils. These authors did not obtain as high percentages of basophils as we have reported, but, when they gave increasing amounts of thyroxin, the percentages of basophils in the anterior lobes were progressively reduced. They concluded that such increased percentages of basophils were correlated with increased secretions of thyroid-stimulating hormone. In the production of thyroid adenomas by feeding their Brassica seed diet, Griesbach, Kennedy and Purves<sup>13</sup> (1945) described changes in the pituitary glands which included increased basophilia with mitosis and a reduction in numbers and in granulation of the acidophils. The weights of the pituitaries did not increase.

The studies of Dempsey and Wislocki<sup>4</sup> (1945) are of interest in their bearing on our own observations. They

have studied the cytoplasmic basophilia, not only of the pituitary but of the placenta as well, with respect to the chemical nature of the substances which gave these tinctorial reactions. They studied sections of pituitary glands of rats which were incubated in solutions of crystalline ribonuclease and learned that the basophilia, so evident after staining with eosin-methylene blue, was abolished by digesting the glands with ribonuclease. Brachet<sup>1</sup> (1940) showed that treatment with ribonuclease abolished the cytoplasmic basophilia of cells of the pancreas, intestine and nervous system. Likewise, Desclin<sup>5</sup> (1940) had shown that the basophilia of the pituitaries of rats detectable by toluidine blue, which increased in concentration during pregnancy and after treatment with estrogens, was abolished by treating sections with a crude extract containing ribonuclease.

Since basophilia is abolished by the enzyme, ribonuclease, it is concluded that basophilia must be attributed to the presence of ribonucleic acid, shown to be active in protein synthesis. Ribonucleic acids are more abundant in immature than in mature cells, and Greenstein<sup>8</sup> (1944) concluded that the ribonucleic acids function in the synthesis of the cellular proteins.

Accordingly, the increased basophilia which we have encountered in the pituitaries of our animals may indicate increased nucleic acid content and thus increased protein synthesis with increased cellular secretions. Although we have not employed the technic of Dempsey and Wislocki<sup>4</sup> (1945), and thus do not know the effect of ribonuclease upon the basophilia encountered, we have reason to believe that there was presumably an increase in the nucleic acids and an increase in the synthesis of the specific secretions in the pituitary cells. We do not know that thyrotropic hormone was released

in increased amounts as a result of this increased basophilia. And yet, objectively, the marked degrees of exophthalmos encountered and the extreme hyperplasia of the thyroid epithelium are physiologic reactions which postulate increased elaboration of hormone.

Wolfe's recent studies<sup>25</sup> (1948) sustain the earlier conclusions that cytoplasmic basophilia is associated with the secretory activity of the cells of the anterior lobe of the pituitary. Wolfe showed that when rats were given estrogens the acidophils became degranulated and by proper staining were found to contain basophilic substance. Likewise, chromophobes were characterized by a cytoplasmic basophilia. Wolfe showed, too, that this basophilia of both degranulated acidophils and chromophobes induced by administration of estrogen was abolished by ribonuclease, thus demonstrating the presence of ribonucleic acid in these cells.

**Summary.** A study of basophilia which developed in the anterior lobes of pituitary glands of rats fed known percentages of 3 well-known goitrogens, in a standard ration, for periods up to 90 days, is reported. All test animals, taking the goitrogens, showed greatly hyperplastic thyroid glands and lowered basal metabolic rates, indicating the lowered concentrations of thyroxine in the blood which these goitrogens are known to induce, by their influence upon the uptake of iodine and its conversion into diiodotyrosine within the thyroid gland.

Basophilia was first significantly evident in pituitaries of animals fed the goitrogens for 72 hours. The percentage of basophils, of all cells counted at that time, ranged from 35.3 to 40.1 and was significantly higher than the percentage of 29 established for the control group of animals at that interval. The per-

centage of basophils progressively increased during the remaining weeks of the experiment, so that at 90 days, the percentages of basophils ranged from 82.4 to 87.8.

This extreme basophilia—higher than any hitherto recorded—we believe, is correlated with increased synthesis and elaboration of hormone. Direct and

conclusive evidence for this conclusion is not available, but systemic reactions such as extreme exophthalmos (Dobyns<sup>6</sup>, 1946) and thyroid hyperplasia, known to be induced by increased amounts of thyroid-stimulating hormone, both indicate increased synthesis of this hormone by the greatly increased numbers of basophilic cells.

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# THE TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH PENICILLIN

A STUDY OF 125 CONSECUTIVE CASES, WITH 73% RECOVERY

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In 1945 we<sup>1</sup> reported a series of 67 cases of pneumococcic meningitis treated with penicillin. Of these 67 patients 26 recovered and 41 died, representing a recovery rate of 39%. It was evident from the report that the problem of therapy in this disease required further investigation. The study was therefore continued in the present series of 125 cases of pneumococcic meningitis and forms the basis of this paper.

**MATERIAL.** There are 125 consecutive cases in this series and they were seen between June 13, 1944, and October 20, 1948. The diagnosis was definitely established in each instance by culturing or typing the organism from the spinal fluid.

**CLINICAL ASPECTS.** Most of the patients presented the typical picture of meningitis on admission. The individ-

ual patients showed considerable variation in the severity of the disease, but most of them appeared critically ill.

There was a wide range in age. (See Table 1.)

In this series of cases a primary focus was established in 78 instances. A definite focus in the ear, mastoid or both was found in 36 of the cases. While this series shows a record of only 6 instances of definite sinusitis, it is possible that this condition existed more frequently than it was recognized. In 27 patients the presence of pneumonia was regarded as the probable primary focus. There were 7 cases of head injury with a fracture through a sinus, mastoid or base of the skull in 5 instances. In 2 cases the meningitis followed cellulitis of the face. There remained 47 cases in which the meningitis was preceded either by no obvious illness or by a simple upper respiratory infection.

**BACTERIOLOGIC DIAGNOSIS.** Diagnostic lumbar punctures were performed in all the cases on admission. The cerebrospinal fluid showed varying degrees of turbidity. The cells were greatly increased in number with polymorphonuclears predominating. In the majority of instances the protein content was moderately to greatly increased. Sugar was either absent or considerably diminished in all cases. Stained smears of the cerebrospinal fluid showed vary-

TABLE 1. RECOVERIES IN RELATION  
TO AGE.

| Number of<br>Age<br>Years | Recoveries and<br>Number of<br>Cases | Deaths in<br>Number of<br>Recoveries | Each Group<br>Number of<br>Deaths |
|---------------------------|--------------------------------------|--------------------------------------|-----------------------------------|
| Under 1                   | 28                                   | 22                                   | 6                                 |
| 1 to 10                   | 16                                   | 15                                   | 1                                 |
| 11 to 20                  | 7                                    | 7                                    | 0                                 |
| 21 to 30                  | 14                                   | 13                                   | 1                                 |
| 31 to 40                  | 9                                    | 7                                    | 2                                 |
| 41 to 50                  | 23                                   | 19                                   | 4                                 |
| 51 to 60                  | 17                                   | 8                                    | 9                                 |
| 61 to 70                  | 8                                    | 0                                    | 8                                 |
| 71 to 80                  | 2                                    | 1                                    | 1                                 |
| 81 to 90                  | 1                                    | 0                                    | 1                                 |
| Total                     | 125                                  | 92                                   | 33                                |

ing numbers of Gram-positive diplococci in 101 instances. Pneumococci were grown from the fluid in 120 of the cases. The organisms were typed in these cases from the cultures and in many instances directly from the spinal fluid. In the 5 cases with negative cultures, the pneumococcus was identified by direct typing from the spinal fluid.

Many strains of pneumococci were represented in the series. There was an apparent relationship between meningitis due to Type 3 and an otitic infection as shown by the fact that of 15 cases due to this type, the primary focus was otogenic in 11 instances. Blood cultures were made in 62 cases prior to the institution of sulfonamide and penicillin therapy. These were positive in 28 instances.

Penicillin sensitivity determinations were made on 75 strains. The range of sensitivity of the organisms is shown in Table 2. The marked susceptibility of these organisms to penicillin is quite apparent.

TABLE 2. PENICILLIN SENSITIVITY OF PNEUMOCOCCI-75 STRAINS

| Range of Sensitivity<br>Units Penicillin per ml. | Number of Strains |
|--|-------------------|
| Under 0.001                                      | 0                 |
| 0.001-0.004                                      | 33                |
| 0.005-0.016                                      | 39                |
| 0.02-0.06  | 3                 |
| Over 0.06  | 0                 |
| Total  | 75                |

TREATMENT. In this series penicillin was administered intrathecally in all but 2 instances. In addition, all the patients were treated with penicillin intramuscularly and most of them received also a sulfonamide, usually sulfadiazine. There was considerable variation in the intrathecal and intramuscular dosages of penicillin as well as in the number of intraspinal injections and the duration of intramuscular treatment. The schedule of penicillin therapy finally evolved is shown in Table 3.

TABLE 3. PENICILLIN DOSAGE SCHEDULE IN PNEUMOCOCCIC MENINGITIS

| Age                                | Intrathecal<br>Units per<br>Injection | Injections | Intramuscular<br>Units<br>Per Day | Days of<br>Treatment |
|------------------------------------|---------------------------------------|------------|-----------------------------------|----------------------|
| Up to<br>4 years                   | 25000-50000                           | 3-5        | 400,000                           | 7-10                 |
| Older<br>Children<br>and<br>Adults | 50000-100000                          | 3-5        | 800,000                           | 7-10                 |

In 8 cases an attempt was made to treat the patient with penicillin given intramuscularly but not intraspinally. In addition these patients received sulfadiazine. A satisfactory response was obtained in only 2 of these cases. In the remaining 6 instances there was a failure of response requiring the additional use of intrathecal penicillin. It is necessary to mention also that in 10 instances mastoidectomy was performed.

RESULTS. In this series of 125 cases there were 92 recoveries and 33 deaths, a recovery rate of 73%. It will be seen from Table 1 that among 97 cases under 51 years of age there were only 14 deaths, whereas among 28 cases above that age there were 19 deaths. It is clear then that the prognosis was decidedly worse in the older age groups. It is important to note that among the fatalities there were 7 cases in which adverse contributory factors were present. These included 3 instances with inadequate intraspinal penicillin therapy, 2 cases complicated by a secondary *B.pyocyaneus* meningitis, a case with acute bacterial endocarditis, and a case associated with multiple severe injuries. In addition, 5 of the patients died within 24 hours following the institution of penicillin therapy.

SPINAL FLUID CHANGES DURING THE COURSE OF TREATMENT. With the institution of penicillin therapy a fairly prompt disappearance of the pneumococci was noted in the vast majority of

the cases. However, as pointed out in a previous paper<sup>1</sup> the early disappearance of the organisms could not be relied upon as an indication of the control of the infection. A more dependable index is the return of the sugar to normal.

Repeated determinations of the concentration of penicillin in the spinal fluid were made in 94 instances. These showed enormous variations and could not be correlated with the clinical results.

**COMPLICATIONS AND REACTIONS DUE TO INTRATHECAL PENICILLIN.** In this series of cases a reaction attributable to the intrathecal administration of penicillin was encountered in several instances. The data relating to these reactions are shown in Table 4. It may be noted that arachnoiditis followed by subarachnoid block occurred in only one instance, and irritative cerebral phenomena were encountered in 4 cases. The outstanding irritative symptoms consisted of pyrexia, delirium and convulsions which occurred within a few hours after the intrathecal injection of the drug. It will be seen from the table that this type of reaction was induced in 3 instances by dosages of 50,000 to 100,000 units of the drug and, in one instance, by an inadvertent injection of 500,000 units. Following the subsidence of the reaction, 2 of the patients were able to tolerate smaller doses of penicillin intraspinally without untoward effect. With regard to the

fatalities, it may be noted that in the case with subarachnoid block the death was unrelated to the reaction while in the other instance the fatal issue appeared to be closely related to the reaction.

In addition there were 4 instances of a secondary meningitis due to *B. pyocyaneus* introduced during the intrathecal administration of penicillin.

**RELAPSES.** It is well known that pneumococcic meningitis may on occasion relapse. In the present series this occurred in only 3 instances, in 2 of which intraspinal penicillin had not been used prior to the relapse. Following a short course of adequate intraspinal penicillin therapy these 3 patients recovered completely.

**SEQUELAE.** In this series there were 4 instances of serious damage to the brain resulting in hydrocephalus, mental impairment or paralysis. These were all in infants under 1 year of age. In one of these, a 3-month old infant, spinal block was present before treatment was begun, necessitating intraventricular therapy. There were also 4 cases of deafness partial or complete.

**Comment.** It is clear from this study that the adequate use of penicillin intrathecally and intramuscularly was highly effective in the treatment of a good majority of the cases of pneumococcic meningitis. Although it could not be stated with certainty that the larger intrathecal doses of penicillin were necessarily more effective than

TABLE 4. REACTIONS IN 5 CASES ATTRIBUTABLE TO INTRATHECAL PENICILLIN.

| Age    | Previous Intraspinal Penicillin<br>No. of<br>Injections | Units per<br>Injection | Dose of Injection<br>Preceding Reaction | Nature of<br>Reaction                 | Outcome   |
|--------|---|------------------------|---|---------------------------------------|-----------|
| 65 yrs | 8   | 20,000                 | Developed progressively.                | Arachnoiditis,<br>block               | Died      |
| 8 yrs  | 9   | 20-100,000             | 100,000                                 | Convulsions                           | Recovered |
| 4 mos  | none  |                        | 50,000                                  | Pyrexia, Convulsions                  | Died      |
| 32 yrs | 3   | 50-100,000             | 500,000<br>(by error)                   | Pyrexia, delirium,<br>pulmonary edema | Recovered |
| 14 yrs | 3   | 50,000                 | 50,000                                  | Pyrexia, convulsions                  | Recovered |

the smaller ones, it was nevertheless our impression that the employment of these larger doses contributed materially to the recovery of a number of patients. Contrary to the general belief, the larger intraspinal doses of the drug have with very few exceptions been well tolerated. It has already been pointed out that the prognosis was decidedly worse in the older age groups. On the other hand there was no evidence of a correlation between the primary focus of infection and the outcome.

Attention has recently been drawn to the hazards of intrathecal penicillin therapy. It has been noted that the antibiotic may lead to the development of an arachnoiditis which may cause spinal block or the appearance of varying degrees of motor or sensory disturbances. In our experience these are rare complications and when they occur are rarely permanent. However, it is extremely important to discontinue the intraspinal administration of penicillin in the presence of subarachnoid block or following the appearance of symptoms of myelopathy in order to prevent the development of irreversible spinal cord changes.

The intrathecal use of penicillin may on occasion cause irritative cerebral reactions, particularly convulsions. As a rule these irritative symptoms clear up rapidly. It should be noted that in the 2 cases in which subsequent intrathecal therapy seemed necessary it was possible to use smaller doses of the drug without any untoward effect.

Although the introduction of a second meningeal infection during the course of intrathecal therapy is of rare occurrence, it must nevertheless be kept in mind. In order to prevent this complication it is very important to guard against contamination in the process of dissolving and administering the penicillin. In two of the cases complicated by a second meningeal infection

the source of the organism was traced to penicillin solutions contaminated by syringes used to withdraw the drug for injection. The details of that investigation were reported in a recent paper by Harris<sup>2</sup> and her collaborators.

The rare occurrence of an untoward effect or complication following the intraspinal use of penicillin should not be a deterrent to the employment of this valuable procedure.

The treatment of pneumococcic meningitis without intrathecal penicillin was recently advocated by Lowrey and Quilligan<sup>3</sup>. These authors reported a group of 17 cases of the disease treated with intramuscular but without intraspinal penicillin, in conjunction with sulfadiazine. Fourteen of these patients recovered. These results are impressive, but their series is too small for definite conclusions. As mentioned previously, an attempt to treat 8 patients in the current series without intraspinal penicillin proved successful in only 2 instances. It would seem unwise at present to rely solely on the intramuscular use of the antibiotic. However, treatment without intrathecal penicillin deserves further investigation.

In this study it was difficult to evaluate properly the role of the adjunctive use of sulfadiazine. It is of interest to note that mastoidectomy seemed necessary in but a small number of cases.

With regard to sequelae it has already been noted that all patients who had serious brain damage were infants less than a year of age. In one of these infants spinal block was present before therapy was instituted. In the cases reported by Lowrey and Quilligan<sup>3</sup>, there were 2 instances of brain damage, although the patients had not received intrathecal therapy. It is obvious, therefore, that neurologic sequelae can be the direct result of the meningeal infection. To what extent, if any, intrathecal penicillin contributes



toward the development of such residua is a matter of speculation. However, these sequelae constitute a serious problem which requires intensive study.

**Summary and Conclusions.** 1. In 125 consecutive cases of pneumococcic meningitis, penicillin was administered intrathecally in all but 2 instances. In addition, all the patients were treated with penicillin intramuscularly and most of them received also a sulfonamide, usually sulfadiazine.

2. The method of treatment and dosage have been described. It was found that, with few exceptions, the larger intrathecal doses of penicillin have been well tolerated.

3. Of the 125 patients, 92 recovered and 33 died, representing a recovery rate of 73%. The prognosis was decidedly worse in the older age groups.

4. An attempt to treat 8 patients with intramuscular but without intraspinal penicillin, in conjunction with sulfadiazine, proved successful in only 2 instances.

5. In this series there were only a few instances in which a complication or reaction was attributable to the intrathecal administration of penicillin. The rare occurrence of such a reaction or complication should not be a deterrent to the administration of penicillin intraspinally.

6. Neurologic sequelae were encountered in a small number of cases. The instances of serious brain damage were all in infants under 1 year of age.

7. In this series it was difficult to evaluate properly the role of the adjunctive use of sulfadiazine.

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# THE CHEMICAL COMBINATION OF INSULIN WITH MUSCLE (DIAPHRAGM) OF NORMAL RAT\*

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THE chemical or physical mechanisms by which hormones affect metabolic reactions in mammalian tissue have so far escaped recognition. For example, it is easy to demonstrate marked effects of insulin upon tissue metabolism, but no one has conclusively shown how these results are brought about. It is obvious that herein lies a fundamental problem of diabetes, whose solution would contribute greatly to our understanding of the disease.

The most popular current assumption is that insulin affects the milieu of tissue enzymes which catalyze the multiple reactions concerned in the metabolism of fat, proteins, and carbohydrate. The possibility of narrowing the search to one or perhaps a few enzymes is greatest when the enzyme preparation is cell-free. Naturally, many experiments have been done with such systems, but, to date, few demonstrations of insulin effects in cell-free systems have been reported and these have been difficult to reproduce.

In sharp contrast to this situation, effects of insulin upon the metabolism of intact cells are easily demonstrated.

The systems used may vary from the intact animal to some isolated surviving tissue such as the intact perfused heart, or the rat diaphragm. As is well known, the latter, when equilibrated aerobically with glucose, utilizes glucose and synthesizes glycogen more abundantly in the presence of insulin. Regardless of whether or not intact cellular morphology is an obligatory requirement for insulin action, the first step in the action of insulin in cellular systems must be its entrance into, or attachment to, some morphological element of the intact cell. We have investigated this phase of the action of insulin and have demonstrated a direct chemical combination of insulin with the intact muscle cell by the following exploratory experiment:

A hemidiaphragm from a normal rat was equilibrated for 1 minute in a phosphate-saline medium containing 0.1 unit of insulin per ml. The diaphragm was then removed and washed twice in a large volume of medium. It was finally equilibrated in medium containing glucose *but no added insulin*. At the end of 90 minutes the final

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glycogen content of the diaphragm was determined. The companion hemidiaphragm was treated in exactly the same way except for the omission of the insulin during the initial 1-minute period. Invariably the hemidiaphragm which had been exposed to insulin for this brief period synthesized more glycogen than the control.

The successive transfers diluted the insulin in the original medium to a final concentration of  $10^8$  units per ml., much too insignificant to have any effect on the diaphragm. We interpret these exploratory experimental results to indicate that (a) during the preliminary 1-minute exposure insulin combines chemically with some constituent of the muscle cell and (b) the combined insulin exerts its customary effect in stimulating glycogen synthesis from glucose.

These conclusions have been abundantly supported by innumerable subsequent experiments which are outlined in this and the accompanying paper.

**Methods.** *Rats.* Male albino rats of the Wistar strain were used. Unless otherwise noted, the rats were sacrificed by decapitation 24 hours after the last feeding.

**Medium.** This had the following composition: 0.040 M sodium phosphate, 0.087 M sodium chloride, 0.005 M magnesium chloride, pH 6.8.

**Insulin.** Unless otherwise stated, this was Lilly amorphous insulin powder (Lot No. W1302). It was dissolved in the medium at the desired final concentration.

**Glucose.** Unless otherwise stated, this was present at a concentration of 0.2% only during the 90 minute assay period.

**Method of Handling Diaphragms.** The following pattern developed quickly and became the norm of the experiments. Modifications of this norm are noted in detail. Two operators performed the various operations in each experiment. They alternated in positions and operations for each rat so as to distribute unconscious bias in handling technique. Following decapitation, the abdomen of the rat was opened and the abdominal aspect of the diaphragm exposed. The ensiform process was lifted and a small nick made in the

diaphragm, causing it to balloon out. The diaphragm was cut along the thoracic border and around the great vessels so that there was no gross bleeding. Alternately right and left hemidiaphragms were used as control and test tissue respectively.

**Equilibration With Insulin.** After removal the hemidiaphragms were weighed on a torsion balance and kept temporarily on the edge of small beakers. The beakers contained 2 ml. of phosphate-saline medium. Insulin was present in one at a given concentration. The diaphragms were now simultaneously placed in their respective media and agitated by rotation for a given time. The temperature during equilibration with insulin was  $25 \pm 1^\circ$  C. unless otherwise noted.

**Washing Period.** Following the equilibration with insulin the diaphragms were removed from the beakers with small forceps. The accumulated hanging drop of medium was removed by touching to filter paper. Each diaphragm was placed in 25 ml. of medium and agitated for 30 seconds. The diaphragms were then removed, the excess medium drained as before, and the washing procedure repeated once. It was calculated that the insulin in the original medium was diluted approximately  $10^7$  times by this procedure.

**Assay Period.** Each hemidiaphragm was then placed in a suitable vessel (usually a Warburg vessel) containing 2 ml. of phosphate-saline medium with added glucose. The medium in the assay period was identical for each hemidiaphragm, viz., phosphate-saline medium plus 0.2% glucose, unless otherwise stated. The vessels were gassed with 100% oxygen and placed in a water bath at  $38^\circ$  C. and shaken for 90 minutes. The hemidiaphragms were then removed and analyzed for glycogen. In some experiments oxygen uptake and glucose utilization were determined during the assay period. Oxygen uptake was determined by the conventional Warburg method. In experiments in which glucose utilization was measured the initial and final glucose content of an aliquot of the medium was determined after deproteinization with  $\text{ZnSO}_4$  and  $\text{Ba(OH)}_2$ .

**Presentation of the Data.** The experiments in this and the accompanying paper were designed to study the influence of various factors upon the chemical combination of insulin with muscle tissue occurring during a brief preliminary equilibration period. It is assumed that an enhanced ability of the test hemidiaphragm, compared to the control, to synthesize glycogen or utilize glucose during a subsequent assay period (no added insulin being present) is proof of this combination.

For the sake of brevity this effect is termed the "insulin effect": *i.e.*, the final glycogen of test hemidiaphragm less that of control hemidiaphragm. Glucose utilization and oxygen uptake are expressed as micromoles per gram wet weight of diaphragm. Glycogen is expressed in all cases as micromoles of glucose equivalent per gram wet weight. For the sake of completeness, the final glycogen content of the control hemidiaphragm is recorded in Table 1. The final glycogen contents of the control hemidiaphragms in the later experiments were close to those reported in Table 1 and have therefore not been included in the tables. The glycogen synthesized may be approximated by subtracting 5  $\mu$ M/gm. which is the mean initial glycogen content under the conditions of our experiments. The mean insulin effects recorded are the means of the paired differences of the final glycogen contents of the experimental and control hemidiaphragms. The standard error of the mean is calculated in all cases. To determine

periods of time. At this concentration, a small but significant increase in glycogen synthesis was obtained after equilibration for 10 seconds. The maximum insulin effect occurred after equilibration for 1 minute. Increasing the time of equilibration beyond 1 minute does not cause any increase in the insulin effect. These findings demonstrate the extreme rapidity of the combination of insulin with the diaphragm.

The mean final glycogen content of the control hemidiaphragm after 90 minutes' equilibration is approximately 15  $\mu$ /gm. Since the initial glycogen content of the fasted rat diaphragm is about 5.0 micromoles per gram, the control diaphragm synthesized approxi-

TABLE 1. THE EFFECT OF TIME OF EQUILIBRATION ON THE COMBINATION OF INSULIN WITH THE ISOLATED RAT DIAPHRAGM

Equilibration with insulin: 0.1 unit per ml; time indicated below. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Time of Equilibration With Insulin | No. of Experiments | Mean Final Glycogen, Control Hemidiaphragm, as Micromoles Glucose/gm. | ASSAY PERIOD   |          |          |
|------------------------------------|--------------------|---|--|----------|----------|
|                                    |                    |   | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | <i>t</i> | <i>P</i> |
| 10 seconds                         | 3                  | 15.3 $\pm$ 0.25   | + 2.0 $\pm$ 0.41   | 4.9      | < 0.05   |
| 1 minute                           | 45                 | 19.3 $\pm$ 0.61   | + 5.8 $\pm$ 0.54   | 10.7     | < 0.001  |
| 5 minutes                          | 6                  | 15.9 $\pm$ 1.00   | + 5.3 $\pm$ 1.01   | 5.3      | < 0.01   |
| 15 minutes                         | 3                  | 16.2 $\pm$ 0.27   | + 4.5 $\pm$ 0.45   | 10.0     | < 0.01   |
| 30 minutes                         | 10                 | 16.3 $\pm$ 1.35   | + 5.0 $\pm$ 1.45   | 3.4      | < 0.01   |

whether an effect of insulin is significantly different from zero, the value of Fisher's *t* was calculated. The probability (*P*) corresponding to this *t* and to the degrees of freedom involved (*N*-1) is recorded in the tables. In general a value of *P* = < 0.05 is regarded as supporting the hypothesis that the insulin effect is significantly different from zero; in other words, that insulin has combined with the muscle during the preliminary period.

**Results. Effect of Time of Equilibration With Insulin at Constant Insulin Concentration.** In Table 1 are reported experiments in which diaphragms from 24-hour fasted rats were equilibrated in a phosphate-saline medium with 0.1 unit of insulin per ml. for varying

mately 10 micromoles of glycogen. The results with the test hemidiaphragms show that preliminary exposure for 1 minute or longer to insulin at 0.1 unit/ml. increased glycogen synthesis 50% over the controls.

**The Effect of Varying the Concentration of Insulin at a Constant Time of Equilibration.** When the period of equilibration with insulin was kept constant at 1 minute, there was an increase of the subsequent insulin effect on glycogen synthesis when the insulin concentration was increased from 0.01 unit per ml. to 1 unit per ml. Equilibration with insulin at a concentration

of 1 unit per ml. for 1 minute brought about an increase in the subsequent glycogen synthesis which was close to that obtained in experiments in which insulin was present during the entire period of equilibration with glucose.

**Insulin Effect with Different Types of Insulin.** The rapid combination of insulin with muscle cells occurs with a wide variety of insulin preparations. The data in Table 3 shows that Lilly amorphous, Lilly protamine-Zn-insulin, a special Zn-free insulin (obtained through the kindness of Dr. Sahyun of

Frederick Stearns and Co.), or Danish Novo insulin each brought about a highly significant insulin effect on glycogen synthesis in the assay period.

**The Effect of pH During Equilibration with Insulin.** Diaphragms were equilibrated with and without insulin at 0.1 unit per ml. for 1 minute in the usual phosphate-saline medium adjusted to different pH values. The diaphragms were washed with medium of pH 6.8 and the final glycogen determined after 90 minutes' equilibration in medium of pH 6.8 containing 0.2%

TABLE 2. THE EFFECT OF CONCENTRATION ON THE COMBINATION OF INSULIN WITH THE ISOLATED RAT DIAPHRAGM

Equilibration with insulin: 1 minute at the concentrations noted below. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Concentration of Insulin, Units per ml. | No. of Experiments | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | ASSAY PERIOD |         |
|---|--------------------|--|--------------|---------|
|   |                    |  | <i>t</i>     | P       |
| 0.01                                    | 7                  | + 0.7 ± 0.40   | 1.8          | > 0.1   |
| 0.10                                    | 45                 | + 5.8 ± 0.54   | 10.7         | < 0.001 |
| 0.50                                    | 8                  | + 6.8 ± 1.04   | 6.5          | < 0.001 |
| 1.00                                    | 8                  | + 9.8 ± 1.11   | 8.8          | < 0.001 |

TABLE 3. THE COMBINATION OF DIFFERENT TYPES OF INSULIN WITH THE ISOLATED RAT DIAPHRAGM

Equilibration with insulin: 1 minute at the concentrations noted below. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Type of Insulin            | Units/ml. | No. of Experiments | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | ASSAY PERIOD |         |
|----------------------------|-----------|--------------------|--|--------------|---------|
|                            |           |                    |  | <i>t</i>     | P       |
| Lilly powdered insulin     | 0.1       | 46                 | + 5.8 ± 0.54   | 10.7         | < 0.001 |
| Zn-free insulin (Stearns') | 0.1       | 6                  | + 4.2 ± 0.48   | 8.8          | < 0.001 |
| Novo insulin               | 0.1       | 3                  | + 6.5 ± 0.21   | 31.0         | < 0.01  |
| Protamine-Zn-insulin       | 1.0       | 6                  | + 8.5 ± 1.91   | 4.5          | < 0.01  |

TABLE 4. THE EFFECT OF pH ON THE COMBINATION OF INSULIN WITH THE ISOLATED RAT DIAPHRAGM

Equilibration with insulin: 1 minute at 0.1 unit per ml. at values of pH noted below. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| pH During Equilibration With Insulin | No. of Experiments | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | ASSAY PERIOD |         |
|--------------------------------------|--------------------|--|--------------|---------|
|                                      |                    |  | <i>t</i>     | P       |
| 5.7                                  | 6                  | + 7.0 ± 1.11   | 6.3          | < 0.01  |
| 6.8                                  | 46                 | + 5.8 ± 0.54   | 10.7         | < 0.001 |
| 8.3                                  | 9                  | + 4.3 ± 0.93   | 4.6          | < 0.01  |

glucose. The data of Table 4 show that there was no significant alteration of the extent of combination of insulin with diaphragm over the pH range of 5.7 to 8.4.

*The Effect of Temperature on the Combination of Insulin with Diaphragm.* In Table 5 are reported experiments in which the equilibration with insulin was carried out at different temperatures. The temperature of the assay period was not altered. There was a definite increase of the insulin effect with increasing temperature during the equilibration with insulin. An increase in temperature apparently causes more insulin to combine with the diaphragm.

content after the usual 90-minute aerobic equilibration in medium containing 0.2% glucose was then determined. In 3 experiments a mean insulin effect of  $5.7 \pm 1.12$  micromoles per gram per 90 minutes was found, a value not different from aerobic controls.

*Effect of Varying the Composition of the Medium.* In almost all of the experiments reported here the equilibration of the diaphragm with insulin was carried out in the standard phosphate-saline medium of pH 6.8. In experiments, not tabulated, the equilibration with insulin (1 minute, 0.1 unit per ml.) was carried out in media of varying composition. The composition of the washing solutions and of the

TABLE 5. THE EFFECT OF TEMPERATURE ON THE COMBINATION OF INSULIN WITH THE ISOLATED RAT DIAPHRAGM

Equilibration with insulin: 1 minute at 0.1 unit per ml. at the temperatures noted below. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Temperature of equilibration With Insulin, ° C. | No. of Experiments | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | ASSAY PERIOD |           |
|---|--------------------|--|--------------|-----------|
|   |                    |  | <i>t</i>     | <i>P</i>  |
| 0   | 4                  | $+ 2.5 \pm 0.74$   | 3.4          | $< 0.05$  |
| 25  | 46                 | $+ 5.8 \pm 0.54$   | 10.7         | $< 0.001$ |
| 38  | 4                  | $+ 6.8 \pm 0.33$   | 20.6         | $< 0.001$ |

*The Effect of Anaerobiosis on the Combination of Insulin with the Diaphragm.* In order to determine whether the presence of oxygen is necessary for the combination of insulin with diaphragm to take place, experiments were done in which diaphragms were equilibrated with insulin under anaerobic conditions. Diaphragms were equilibrated in phosphate-saline medium at 25° C. for 5 minutes in vessels gassed with nitrogen. Insulin was then added to one vessel to give a concentration of 0.1 unit per ml. The experimental and control diaphragms were then equilibrated anaerobically for another minute. They were rapidly removed and washed twice in 25 ml. portions of medium. The final glycogen

medium during the assay period were unchanged. Substitution of the standard phosphate medium with 0.15 M NaCl, 0.3 M sorbitol, phosphate-saline medium in which 75% of the cations were potassium, or phosphate-saline medium containing 0.2% glucose did not result in any significant differences in the effects of insulin observed.

*Effects of Prolonged Washing Following the Equilibration with Insulin.* In the standard procedure there were 2 half-minute washings in 25 ml. of phosphate-saline medium. In order to study whether insulin combined to the diaphragm can be removed by prolonged washing a number of experiments were carried out in which the diaphragms were equilibrated in phos-

phate-saline medium for extended periods of time subsequent to the exposure to insulin. After equilibration with insulin the diaphragms were washed for 1 minute in 25 ml. phosphate-saline medium in order to remove insulin adhering superficially to the diaphragm. They were then transferred to another portion of 25 ml. of oxygenated medium and equilibrated for 15, 30, or 60 minutes. The final glycogen contents of the diaphragms were determined after 90 minutes' equilibration in phosphate-saline medium containing 0.2% glucose. The data (Table 6) show that significant effects of insulin were obtained even after washing for 60 minutes. There is apparently a gradual decrease

sible for the insulin effects observed was ruled out as follows: One of the hemidiaphragms was made identifiable by a small nick in the edge. Both test and control hemidiaphragms were placed in the same vessel during the 90-minute assay period following the equilibration of 1 hemidiaphragm with insulin (0.5 units per ml.) for 1 minute. In 3 experiments, when the control and the pretreated hemidiaphragms were compared, a mean insulin effect on glycogen synthesis of  $+ 4.7 \pm 0.95$  was observed. It can be concluded that the traces of insulin carried over into the assay medium were not sufficient to have any significant effect on the glycogen synthesis of the control diaphragm. The experiment also indicates

TABLE 6. COMBINATION OF INSULIN WITH ISOLATED RAT DIAPHRAGM. EFFECT OF PROLONGED WASHING OF DIAPHRAGM FOLLOWING THE EQUILIBRATION WITH INSULIN

Equilibration with insulin: 5 minutes at 0.5 units per ml. Assay period: 90 minutes at 35° C. in a phosphate-saline medium containing 0.2% glucose.

| Time of Washing, Minutes | No. of Experiments | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | ASSAY PERIOD |         |
|--------------------------|--------------------|--|--------------|---------|
|                          |                    |  | t            | P       |
| 1                        | 4                  | $+ 7.8 \pm 0.68$   | 11.5         | < 0.01  |
| 15                       | 5                  | $+ 11.2 \pm 0.84$  | 13.3         | < 0.001 |
| 30                       | 9                  | $+ 4.9 \pm 1.71$   | 2.9          | < 0.05  |
| 60                       | 8                  | $+ 2.9 \pm 1.20$   | 2.4          | 0.05    |

in the insulin effect with increasing time of washing. A long period of washing is necessary, however, in order to abolish the effect of insulin. The decrease in the insulin effect may have been due to a gradual loss of bound insulin but it may also be a reflection of a loss of the ability of the diaphragm to synthesize glycogen or respond to insulin.

*Equilibration of Control and Test Diaphragms in the Same Vessel During the Assay Period.* The possibility that the infinitesimal traces of insulin carried over in the medium adhering to the diaphragm (and, therefore, not chemically bound) might be respon-

that there was not enough loss of bound insulin from the test diaphragm to affect the metabolism of the control diaphragm.

*The Influence of Combined Insulin Upon the Time Course of Glycogen Synthesis.* A striking indication of the persistence of the combination of insulin with the diaphragm is shown in Figure 1. A hemidiaphragm was equilibrated with insulin at 0.1 unit per ml. for 1 minute. Following washing, the test and control hemidiaphragms were equilibrated for varying periods of time in medium containing 0.2% glucose and the final glycogen contents determined. There is a linear increase

of the insulin effect with time, showing that the combined insulin exerted its effects in an unabated fashion for 60 minutes. In other words, there is no indication of a dissociation of the insulin-tissue complex during this time. Comparison with untreated hemidiaphragms during the first 60 minutes shows that the combined insulin has doubled the rate of glycogen synthesis.

*The Effect of Varying the Glucose Concentration During the Assay Period.* The equilibration period with insulin

the higher insulin concentration (upper curve) more insulin is bound and the glucose concentration becomes the limiting factor so that an increase in glucose concentration results in a marked increase in the insulin effect. At the higher glucose concentration the glycogen synthesized in the insulinized hemidiaphragm is double that of the control.

*The Effect of Bound Insulin on Oxygen Uptake, Glucose Uptake and Glycogen Synthesis.* In several experi-

INSULIN EFFECT ON  
GLYCOGEN SYNTHESIS.  
AS MICROMOLES GLUCOSE  
PER GRAM

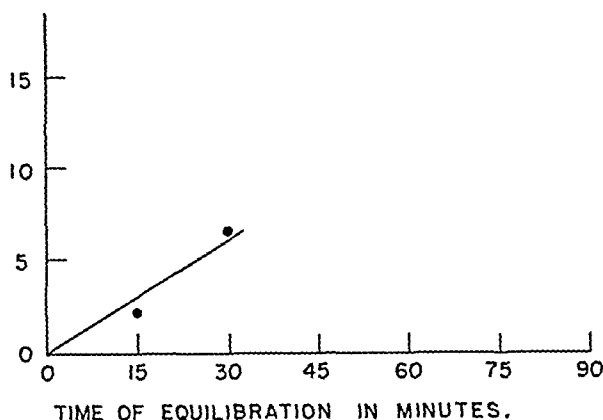


FIG. 1. THE INFLUENCE OF COMBINED INSULIN ON THE TIME-COURSE OF GLYCOGEN SYNTHESIS BY NORMAL RAT DIAPHRAGMS. One minute equilibration with insulin at a concentration of 1 unit per ml. followed by 2 washings in 25 ml. phosphate-saline medium. Final glycogen determined after equilibration for various times in medium containing 0.2% glucose. Each point in the above figure represents the mean of the insulin effect in 4 separate experiments.

was 1 minute and the insulin concentration 0.1 and 1 unit per ml. respectively. The glucose concentration varied from 0.2 to 1.0% during the assay period. The experimental results reported in Figure 2 show that (a) When the insulin concentration was 0.1 unit per ml. (lower curve) there was no significant increase in the insulin effect when the glucose concentration was increased from 0.2 to 1.0%. Apparently the amount of insulin bound becomes the limiting factor in increasing glycogen synthesis. (b) At

ments the analytical measurements were not confined to the determination of glycogen but oxygen uptake and the disappearance of glucose from the medium were also measured during the assay period. In none of these experiments was a significant effect of insulin on oxygen uptake observed. The effect on glycogen synthesis, however, was reflected in a concomitant increase in glucose uptake. This is seen in the results presented in Table 7. There is approximately a 100% increase in both glucose uptake and glycogen synthesis.



It is observed that only about half of the glucose utilized is accounted for as glycogen synthesized in the diaphragm exposed to insulin and in the control.

**Discussion.** It has been demonstrated that the isolated rat hemidiaphragm, after a short preliminary equilibration in a solution containing insulin, exhibits an increased glucose uptake and glycogen synthesis compared to controls. This observation is interpreted to mean that a chemical combination of insulin with structural units of muscle

insulin, the concentration, and on the temperature during equilibration.

A simple diffusion of insulin into the diaphragm appears to be ruled out by the demonstration of the extreme rapidity of the reaction and by its irreversibility, manifested by the preservation of an insulin effect after prolonged washing, and by the sustained action of insulin during the equilibration with glucose.

The speed of the uptake of insulin by the diaphragm is remarkable. Significant effects were obtained after only

INSULIN EFFECT ON  
GLYCOGEN SYNTHESIS.  
AS MICROMOLES GLUCOSE  
PER GRAM

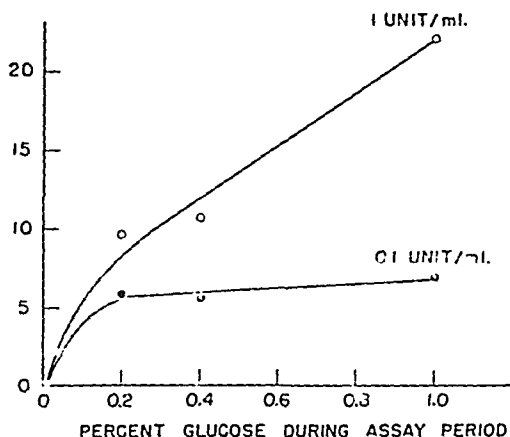


FIG. 2. THE EFFECT OF COMBINED INSULIN UPON THE SYNTHESIS OF GLYCOGEN AT VARYING CONCENTRATIONS OF GLUCOSE. One minute equilibration with insulin at a concentration of 0.1 or 1 unit per ml. followed by 2 washings in 25 ml. medium. Final glycogen determined after 90 minutes equilibration in medium containing different concentrations of glucose. Each point in the above figure represents the mean of the insulin effect in 6 or more separate experiments.

cells of the diaphragm takes place rapidly; that this combination is not easily reversed; and that the combined insulin exerts its customary metabolic effects during the subsequent period of equilibration with glucose.

The concept that a chemical reaction between insulin and some muscle constituent takes place is supported by the observations that the effects of insulin are dependent upon the time of contact of the diaphragm with

10 seconds equilibration and the maximum insulin effect was obtained after about 1 minute. By these findings an effect of insulin has, for the first time, been sharply localized in time.

It is tempting to speculate on the problem of the locus of the attachment of insulin to the diaphragm. The most attractive hypothesis seems to be that it combines with the outer surface of the muscle cells. The question then arises of whether the insulin

TABLE 7. THE EFFECT OF COMBINED INSULIN ON OXYGEN UPTAKE, GLUCOSE UPTAKE, AND GLYCOGEN SYNTHESIS OF THE ISOLATED RAT DIAPHRAGM

Equilibration with insulin: 5 minutes at 0.5 units per ml. Assay period: oxygen uptake, glucose uptake, and final glycogen determined after 90 minutes equilibration at 33° C. in phosphate-saline medium containing 0.2% glucose.

| No. of Experiments. | Oxygen Uptake, Micromoles/gm. |          | Glucose Uptake, Micromoles/gm. |             | Final Glycogen, as Micromoles Glucose/gm. |             |
|---------------------|-------------------------------|----------|--------------------------------|-------------|---|-------------|
|                     | Control                       | Test     | Control                        | Test        | Control                                   | Test        |
| 4                   | 86 ± 4.4                      | 79 ± 4.7 | 16.8 ± 1.66                    | 32.4 ± 1.18 | 13.7 ± 1.43                               | 21.5 ± 1.10 |
| Insulin effect:     | - 7 ± 6.4                     |          | + 15.6 ± 2.04                  |             | + 7.8 ± 1.80                              |             |

exerts its action in metabolism after being further transported into the interior of the cell, or whether the site of attachment on the surface of the cell is also the site at which it exerts its metabolic effects. Such effects could be brought about by an alteration of the permeability of the cell wall to certain metabolites or by a regulation of enzymatic reactions taking place at the cell surface. However, these are questions that cannot be answered at present.

Only the crudest estimation of the amount of insulin bound can be made. If the site of attachment is the cell surface, the insulin must first traverse the covering thoracic or abdominal mesothelium and the sarcolemma. The rate of diffusion through these layers during the short exposure to insulin would then limit the amount which could be chemically bound. Assuming that the muscle substance offers no more impediment than water to the diffusion of insulin it is possible to calculate the amount which could diffuse into the diaphragm during the time of equilibration. A definite insulin effect was obtained in 1 minute when the concentration was 0.1 unit per ml. Under these conditions it can be calculated that the amount which diffuses into the diaphragm is approximately 0.0001 unit per gram of muscle. This estimation, although crude, and based on the assumption that insulin must diffuse into the diaphragm for a considerable distance before it can combine chemically with a muscle constituent, indicates that the amount undergoing chemical combination with the diaphragm is extremely small. This estimate is, of course, a maximum, and the real value may be much less. It is possible to infer, however, that remarkably small amounts of insulin rapidly combining with tissue structures may produce profound changes in metabolism.

Whatever the amount of insulin involved, we have concluded from the findings reported here that the first step in the action of insulin on muscle tissue is a rapid chemical combination with a muscle constituent. The precise meaning of this binding of insulin by muscle tissue in the problems of carbohydrate metabolism and diabetes cannot be discussed without much more experimentation. In the accompanying paper evidence will be given which shows that the phenomenon may be controlled by endocrine factors.

**Summary.** 1. Rat hemidiaphragms in contact with insulin for 1 minute or less show an increased rate of glycogen synthesis and glucose uptake compared to controls when equilibrated for 90 minutes without insulin. This has been interpreted as evidence for a chemical combination of insulin with rat diaphragm.

We wish to express our appreciation to Phyllis Stapley Tuddenham, Mary-Ellen Miller, and William J. King for their expert technical assistance.

2. The combination of insulin with the diaphragm occurred within 10 seconds and reached a maximum at 1 minute. Increasing the concentration from 0.1 to 1.0 unit per ml. resulted in a pronounced increase of the insulin effect.

3. Raising the temperature from 0° C. to 38° C. during the 1 minute equilibration period resulted in an increased combination of insulin with the diaphragm. Changing the pH during this period had no effect.

4. Amorphous, zinc-free, Novo insulin, and protamine insulin proved equally capable of combining with the rat diaphragm.

5. It is concluded that the first step in the action of insulin on the metabolism of intact tissue is a rapid and firm attachment of the insulin molecule to the cell.

# HORMONAL INFLUENCES ON THE CHEMICAL COMBINATION OF INSULIN WITH RAT MUSCLE (DIAPHRAGM)\*

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IN the preceding paper<sup>1</sup> it was shown that insulin combines chemically with muscle tissue (diaphragm) of the rat with remarkable facility. The tissue-insulin combination resists the dissociating action of prolonged washing in the insulin-free medium, and the combined insulin, presumably present in minute amounts, increases the ability of the tissue to utilize glucose and synthesize glycogen. Since no extra insulin is present during the assay period these metabolic effects are presumably due to some physical or chemical action of the combined insulin.

The discovery of this phenomenon raises many questions, foremost among them being whether the combination of insulin with tissue is a prerequisite for its physiological action and whether the combination of insulin with the tissue is influenced by hormonal factors. In the first paper we have studied the influence of a variety of factors on the reaction; in this paper we report the effects of the antecedent removal of endocrine glands, and of the administration of various hormone preparations under different experimental conditions.

The experimental methods and the presentation of the data are identical

with those previously reported<sup>1</sup> and need not be repeated here.

The extent of the combination of insulin with the diaphragm is measured by the increase in glycogen synthesis over the control in the final equilibration without insulin in a phosphate-saline medium containing glucose. A decrease in the insulin effect on glycogen synthesis has been interpreted as evidence for a decrease of the extent of combination with the diaphragm.

*The Combination of Insulin with Isolated Diaphragm from Alloxan-Diabetic, Adrenalectomized, and Hypophysectomized Rats.* The metabolic state induced by injection of alloxan in the rat diminishes the ability of the diaphragm to combine with insulin. This is shown (Table 1) by a sharp diminution of the insulin effect measured in the assay period. The degree of refractoriness to insulin appears to be correlated with the severity of the diabetes as indicated roughly by the level of blood sugar at the time of sacrifice. Somewhat surprisingly, adrenalectomy and hypophysectomy had no effect on the combination of insulin with the diaphragm (Table 1).

*The Combination of Insulin with*

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*Isolated Diaphragm from Rats Injected with Pituitary and Adrenal Cortical Extracts.* A 1:1 extract of whole beef anterior pituitary gland was prepared by grinding the glands with sand and extracting with cold 0.15 M sodium

tracts reported above indicate that one or more pituitary factors are capable of influencing the ability of the diaphragm to combine with insulin. A number of experiments were carried out with more or less purified anterior

TABLE 1. EFFECT OF ENDOCRINE ABNORMALITIES IN THE EXPERIMENTAL ANIMALS ON THE SUBSEQUENT COMBINATION OF INSULIN WITH THE RAT DIAPHRAGM

Equilibration with insulin: 0.1 unit per ml. for 1 minute. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Experimental Animals | No. of Experiments | ASSAY PERIOD   |      |         |
|----------------------|--------------------|--|------|---------|
|                      |                    | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | t    | P       |
| Normal               | 45                 | + 5.8 ± 0.54   | 10.7 | < 0.001 |
| Mild diabetic*       | 10                 | + 2.9 ± 1.22   | 2.4  | 0.05    |
| Severe diabetic*     | 7                  | - 0.1 ± 1.28   |      |         |
| Adrenalectomized†    | 5                  | + 4.9 ± 1.54   | 3.2  | < 0.05  |
| Hypophysectomized§   | 8                  | + 6.1 ± 1.48   | 4.1  | < 0.01  |

\* Rats made diabetic by intraperitoneal injection of 160 mg./kilo of alloxan monohydrate. The group designated as mildly diabetic consisted of rats having blood sugar values less than 500 mg. % at the time of sacrifice. The rats in the severely diabetic group had blood sugar values greater than 500 mg. %.

† Adrenalectomized 6 days before use and maintained on 1% NaCl.

§ Hypophysectomized an average of 1 week before use.

chloride solution. The suspension was centrifuged at 8000 RPM for 5 minutes and the supernatant used. Three ml. was injected intraperitoneally and the rat diaphragm removed after 20 hours. It was found that exposure to insulin at a concentration of 0.1 unit per ml. for 1 minute did not result in a significant insulin effect on glycogen synthesis in the assay period (Table 2). This indicates that the injection of anterior pituitary extract has impaired the ability of the diaphragm to combine with insulin.

Injection of 1 to 4 ml. of adrenal cortex extract (Upjohn) 2 hours prior to the removal of the diaphragm had no effect on the combination with insulin.

*The Combination of Insulin with Isolated Diaphragm from Rats Injected with Purified Pituitary Fractions.* The experiments with crude pituitary ex-

pituitary fractions. It was found that the active principle followed the growth hormone in fractionation procedures and that crystalline growth hormone was active in small doses.

In preliminary experiments beef anterior pituitary glands were fractionated according to the method of Wilhelmi, Fishman and Russell<sup>3</sup>. A fraction corresponding to fraction A + B + C of these authors was obtained by precipitating the alkaline extract of anterior pituitary glands with 24% ethanol at pH 6.8. This fraction contains most of the growth hormone of the original alkaline extract. No effect of insulin was observed in experiments with diaphragms from rats injected 20 hours earlier with 35 mg. of this preparation. The activity of the preparation was destroyed by heating for 10 minutes at 70° C. The heat lability of the active factor corresponds

to that of the growth hormone which is stated to be inactivated by heating to 70 to 80° C.<sup>2</sup>

Further experiments with purified anterior pituitary fractions are recorded in Table 2. The insulin effect on gly-

rats is capable of inhibiting the combination of insulin with the diaphragm.

Among the active preparations was a crystalline growth hormone prepared by Armour and Co. (Lot 22KR2) stated to be the purest preparation so far

TABLE 2. EFFECT OF INJECTION OF ANTERIOR PITUITARY PREPARATIONS ON THE SUBSEQUENT COMBINATION OF INSULIN WITH THE ISOLATED RAT DIAPHRAGM\*

Equilibration with insulin: 0.1 unit per ml. for 1 minute. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Preparation Injected                              | No. of Experiments | Dosage     | Time After Injection, Hours | ASSAY PERIOD   |      |         |
|---|--------------------|------------|-----------------------------|--|------|---------|
|   |                    |            |                             | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | t    | P       |
| Normal controls                                   | 45                 |            |                             | + 5.8 ± 0.54   | 10.7 | < 0.001 |
| 1:1 NaCl extract of beef anterior pituitary gland | 12                 | 3 ml.      | 20                          | + 1.5 ± 0.78   | 1.9  | > 0.05  |
| Adrenal cortex extract (Upjohn)                   | 7                  | 1 to 4 ml. | 2                           | + 3.8 ± 1.15   | 3.3  | < 0.02  |
| Fraction D**                                      | 6                  | 1.3 mg.    | 20                          | + 9.5 ± 1.50   | 6.3  | < 0.01  |
| Fraction E**                                      | 6                  | 5.0 mg.    | 20                          | + 7.1 ± 1.17   | 6.1  | < 0.01  |
| Fraction 380-4**                                  | 5                  | 5.0 mg.    | 3                           | + 8.0 ± 1.77   | 4.5  | < 0.02  |
| Growth hormone†                                   | 6                  | 1.0 mg.    | 2                           | + 3.1 ± 1.37   | 2.3  | > 0.05  |
| Growth hormone†                                   | 6                  | 1.0 mg.    | 20                          | - 0.2 ± 1.35   |      |         |
| Crystalline growth hormone§                       | 6                  | 1.0 mg.    | 3                           | + 2.8 ± 1.43   | 2.0  | > 0.1   |
| Crystalline growth hormone¶                       | 6                  | 0.25 mg.   | 20                          | + 4.8 ± 1.95   | 2.5  | 0.05    |
| Crystalline growth hormone¶                       | 12                 | 0.50 mg.   | 20                          | - 0.1 ± 2.04   |      |         |

\* The purified pituitary fractions were kindly supplied by Dr. A. E. Wilhelmi.

\*\* These fractions had little or no growth hormone activity. Fraction D was obtained from the 24% ethanol fraction at pH 4.6. Fraction E was obtained from the 40% ethanol fraction at pH 4.6. Fraction 380-4 was the precipitate obtained from 0.1 M KCl at pH 5 in the course of crystallization of the growth hormone.

† Lot WP-1, Armour and Co.

§ A crystalline preparation (B-380) stated to be approximately 85% pure.

¶ Crystalline growth hormone. Lot 22KR2, Armour and Co. This preparation is stated to be the best of the Armour preparations so far obtained.

cogen synthesis in the assay period was not significantly different from zero after prior injection of highly purified preparations of growth hormone. However, the injection of 3 different pituitary preparations stated to contain little or no growth hormone did not cause any diminution of the insulin effect. The experiments indicate that growth hormone itself or a factor closely associated chemically with the growth hormone when injected into

obtained by them. Of this substance, 0.5 mg. injected 20 hours previously completely prevented the combination of insulin and diaphragm under the conditions of our experiments. Apparently 0.25 mg. was below the minimum active dose.

The mean insulin effect on glycogen synthesis in the 36 experiments in which highly purified growth hormone preparations were injected was + 1.8 ± 0.83 (t = 2.2, P = 0.03).

This value is significantly different from zero but highly significantly lower than the insulin effect obtained with diaphragms from normal rats.

*In Vitro Effects of Pituitary Preparations on the Combination of Insulin with the Rat Diaphragm.* An interrelation between pituitary factors and insulin was also demonstrated by experiments *in vitro*. Two types of experiments were done: (a) Experiments in which rat diaphragms were equilibrated with insulin in the presence of pituitary preparations. (b) Experiments in which rat diaphragms were equilibrated in a preliminary period with pituitary preparations, washed, and subsequently exposed to insulin. With both types of experiments controls were carried out with different tissue extracts and protein solutions.

In Table 3 are reported the results of experiments in which diaphragms were equilibrated in solutions of vari-

minutes equilibration at 38° C. in medium containing 0.2% glucose.

The crude pituitary extracts were prepared by grinding anterior beef pituitary glands in phosphate-saline medium of pH 6.8. The supernatant obtained after centrifugation at 8000 RPM for 5 minutes was utilized.

No effect of insulin was observed in experiments in which diaphragms were equilibrated with insulin in the presence of 1/3 or 1/10 crude pituitary extracts. When a more dilute extract was used the insulin effect observed was positive, but significantly lower than that obtained in the absence of pituitary extract in the medium. The active principle involved is heat labile since pituitary extracts heated to 70° C. for 10 minutes had no effect on the combination of insulin with the rat diaphragm. That the *in vitro* effect observed with pituitary extract has a certain specificity is indicated by the

TABLE 3. THE COMBINATION OF INSULIN WITH NORMAL RAT DIAPHRAGM IN THE PRESENCE OF VARIOUS SUBSTANCES.

Equilibration with insulin in the presence of the substances indicated: 1 minute at 0.1 unit per ml. Insulin was added to the solutions just before immersion of the diaphragm. Assay period: 90 minutes in a phosphate-saline medium containing 0.2% glucose.

| Experiment  | No. of Rats | ASSAY PERIOD  |          |          |
|---|-------------|---|----------|----------|
|   |             | Mean Insulin Effect<br>on Glycogen Synthesis,<br>as Micromoles<br>Glucose/gm. | <i>t</i> | <i>P</i> |
| Normal controls   | 45          | + 5.8 ± 0.54  | 10.7     | < 0.001  |
| 1:3 pituitary extract                                     | 6           | + 0.8 ± 1.42  |          |          |
| 1:10 pituitary extract                                    | 9           | + 0.5 ± 0.51  |          |          |
| 1:25 pituitary extract                                    | 6           | + 2.4 ± 0.79  | 3.0      | < 0.05   |
| 1:10 pituitary extract heated<br>to 70° C. for 10 minutes | 5           | + 5.0 ± 2.10  | 2.4      | > 0.05   |
| 1:5 rat muscle extract                                    | 6           | + 3.3 ± 0.72  | 4.6      | < 0.01   |
| 1:10 rat brain extract                                    | 6           | + 3.9 ± 0.50  | 7.8      | < 0.001  |
| 1:10 rat liver extract                                    | 4           | + 0.1 ± 0.59  |          |          |
| 2.5% Cohn Fraction V,<br>mainly serum albumin             | 4           | + 0.8 ± 1.07  |          |          |

ous substances with and without added insulin (0.1 unit per ml.). After 1 minute equilibration the diaphragms were washed in the standard way and the final glycogen determined after 90

demonstration that a normal insulin effect was obtained when diaphragms were equilibrated in the presence of concentrated extracts of rat brain or muscle. However, a diminution of the

insulin effect similar to that observed with crude pituitary extract was obtained with 1/10 rat liver extract or with a 2.5% solution of human serum albumin (human plasma fraction V obtained from Dr. E. J. Cohn). It appears that certain substances *in vitro* are capable of preventing the combination of insulin with the rat diaphragm while others are inactive in this respect. Two modes of action of such substances appear possible: (a) The substances combine with insulin and thereby prevent its combination with the diaphragm. (b) The substances combine in some way with the dia-

When pre-equilibrated with the diaphragm, no other substance tested was capable of preventing the subsequent combination of insulin. Serum albumin or rat liver extract which prevented the combination in the presence of insulin were inactive in pre-equilibration experiments.

Preliminary experiments with partially purified anterior pituitary fractions have not enabled us to identify further the factor in crude pituitary extracts which is active *in vitro*.

We have not succeeded in demonstrating an effect *in vitro* of highly purified growth hormone preparations.

TABLE 4. THE EFFECT OF PRE-TREATMENT OF THE DIAPHRAGM FROM NORMAL RATS ON THE SUBSEQUENT COMBINATION WITH INSULIN

Diaphragms pre-equilibrated with the substances indicated and washed once before exposure to insulin. Equilibration with insulin: 1 minute at 0.1 unit per ml. Assay period: 90 minutes at 38° C. in a phosphate-saline medium containing 0.2% glucose.

| Experiment                                       | No. of Rats | Time of Pre-equilibration, Minutes | ASSAY PERIOD   |          |         |
|--|-------------|------------------------------------|--|----------|---------|
|  |             |                                    | Mean Insulin Effect on Glycogen Synthesis, as Micromoles Glucose/gm. | <i>t</i> | P       |
| Normal controls                                  | 45          |                                    | + 5.8 ± 0.54   | 10.7     | < 0.001 |
| 1:10 pituitary extract                           | 6           | 1                                  | + 2.9 ± 0.49   | 5.9      | < 0.01  |
| 1:10 pituitary extract                           | 14          | 5                                  | + 1.0 ± 0.58   | 1.7      | 0.10    |
| 1:10 pituitary extract aged for 1 hour at 38° C. | 6           | 5                                  | + 1.4 ± 0.69   | 2.0      | 0.10    |
| 2.5% Cohn Fraction V, mainly serum albumin       | 7           | 5                                  | + 3.9 ± 1.18   | 3.3      | < 0.02  |
| 1:10 rat liver extract                           | 11          | 5                                  | + 3.8 ± 1.06   | 3.6      | < 0.01  |

phragm and prevent the subsequent combination of insulin.

That the latter mechanism may be the one that is operative in the case of pituitary extract is supported by the finding that the insulin effect on glycogen synthesis after 5 minutes preliminary equilibration in a 1:10 pituitary extract is not significantly different from zero. Pre-equilibration in 1:10 crude pituitary extract for 1 minute significantly lowered the insulin effect (Table 4).

The active principle in the crude pituitary extract is not destroyed by heating for 1 hour at 38° C.

For example, the equilibration of rat diaphragm for 5 minutes in a solution containing 0.5 mg. crystalline growth hormone (22KR2) per ml. had no effect on the subsequent response of the diaphragm to insulin. These observations indicate that the factor in crude pituitary extract active *in vitro* may not be the growth hormone.

**Discussion.** The experiments reported here indicate that the rapid and stable combination of insulin with rat diaphragm can be influenced by pituitary factors. This has been demonstrated *in vivo* and *in vitro*.

Following short exposures to insulin, the isolated diaphragms from rats in-



jected with anterior pituitary preparations responded metabolically to a lesser extent than did normal diaphragms. We have interpreted this finding as evidence for an interference by anterior pituitary factors with the initial combination of insulin with the diaphragm. However, our experiments do not exclude the possibility that the physiological action of combined insulin may be antagonized by pituitary hormones in the diaphragm or that pituitary factors may have an independent action on carbohydrate metabolism of the diaphragm.

The injection of anterior pituitary fractions high in growth hormone activity and of crystalline growth hormone preparations rendered the diaphragm refractory to insulin under the conditions of our experiments indicating that the attachment of insulin to the diaphragm was impaired. It seems certain that the active principle involved is the growth hormone itself or a factor closely related to it chemically.

*In vitro* pre-equilibration with crude anterior pituitary extract also impaired the ability of normal rat diaphragm to combine with insulin. This indicates that some pituitary factor is capable of combining with the rat diaphragm in a manner similar to insulin. In contrast to the *in vivo* experiments, growth hormone preparations were inactive.

Diaphragms from alloxan-diabetic rats showed a diminished response to insulin which could be correlated with the severity of the diabetes. One defect in diabetic muscle may therefore be an impaired ability to combine with insulin, perhaps due to the presence of an excess of pituitary hormones. Diaphragms from adrenalectomized

and hypophysectomized rats combined with insulin in a normal manner.

The general problem of the mechanism of action of hormones on cellular metabolism remains obscure. Our experiments suggest that a combination with tissue constituents may be prerequisite for hormonal action. Whatever the mechanism of action of pituitary hormones, the well known physiological antagonism between insulin and pituitary hormones has been demonstrated in isolated muscle tissue and within sharply defined time limits.

**Summary.** The chemical combination of insulin has been studied in the isolated diaphragm from rats with endocrine abnormalities, or injected with various hormonal preparations. The *in vitro* effect of anterior pituitary hormones on the combination of insulin with the diaphragm has also been studied. The following observations were made:

1. Diaphragms from alloxan-diabetic rats manifested an impaired ability to combine with insulin. Diaphragms from adrenalectomized and hypophysectomized rats did not differ from normal in this respect.

2. Crude anterior pituitary extract or purified growth hormone preparations when injected into the normal rat rendered the diaphragm refractory to combination with insulin. It has been concluded that the active principle is the growth hormone or a factor chemically closely related to the growth hormone.

3. Crude pituitary extracts *in vitro* impaired the ability of the normal rat diaphragm to combine with insulin. Purified growth hormone preparations were inactive *in vitro*.

We wish to express our appreciation to Phyllis Stapley Tuddenham, Mary-Ellen Miller, and William J. King for their expert technical assistance.

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# THE EFFECT OF BODY POSITION AND REFERENCE LEVEL ON THE DETERMINATION OF VENOUS AND RIGHT AURICULAR PRESSURE

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Most studies of venous pressure have been made with the patient in a supine position, but a few investigators have determined venous tension with the subjects in a sitting posture. Early workers<sup>1,6,7</sup> reported an increase in venous tension with the assumption of the sitting position. Lyons, Kennedy, and Burwell<sup>8</sup> found the venous pressure to be slightly higher in 90° than in 45° sitting positions in a group of 50 normal subjects, but they reported no apparent relation between the level of venous pressure and the postural angle in a given individual. Although the level to which venous pressure was referred was usually stated, little attention was given to it in considering changes in venous pressure with body position.

Recently Winsor and Burch<sup>10,11</sup>, using an auricular reference level which they called the "phlebostatic axis", found no significant difference between venous pressure measurements made in supine and various sitting positions in normal subjects. The phlebostatic axis was defined as the line of intersection of a frontal plane passing half the distance from the base of the xiphoid of the sternum and the dorsum of the body with a cross-sectional plane passing through the 4th intercostal space adjacent to the sternum.

The clinical usefulness of venous

pressure measurements would be greatly enhanced in some cases if determinations could be made with the patient in a sitting posture. This is particularly true for patients who are orthopedic and unable to relax in a supine position. Thus, the demonstration that cardiac patients as well as normal subjects show no significant variation in venous tension in different body positions would be of practical importance.

In preliminary experiments it was found that even when the phlebostatic axis of Winsor and Burch was used as a reference level with subjects in a sitting posture, normal individuals showed high venous pressures. Consequently, the present study was undertaken to investigate the effect of changes in posture on venous pressure measurements. Since Burch and associates<sup>2,3,10,11</sup> used a water or an aneroid manometer with an air-filled system for the measurement of venous pressure, a comparison was made between such a manometric system and the manometer of Moritz and von Tabora<sup>9</sup> which was used in this study. The present report also includes data on measurements of right auricular pressure in supine and in 45° sitting postures with use of the technique of cardiac catheterization.

**Experimental Procedures.** Subjects for study were selected from the Infirmary (Old Peo-  
(281)

ple's Home) and the wards of the Baltimore City Hospitals.

1. *Comparison of Manometers.* Venous pressure was measured with the phlebomanometer of Burch and Sodeman<sup>2</sup> and the manometer of Moritz and van Tabora<sup>9</sup> in 31 subjects. These include (a) five normal individuals, (b) 20 patients with various diseases including compensated heart disease, and (c) 6 cases with congestive heart failure.

Each subject rested from 10 to 15 minutes before venous pressure measurements were made. Novocaine (1%) was injected as a local anesthetic before insertion of the needle into the vein. Venous pressure was measured first with the phlebomanometer of Burch and Sodeman.

Without removing the needle from the vein, the adaptor of the phlebomanometer was disconnected and the saline manometer attached to the needle. Venous pressure was measured by allowing saline to run into the vein until equilibrium was reached. The zero point on the manometer was set at the venipuncture level. Determinations were made until 3 readings varied less than 1 cm. of saline; the average of these three readings was recorded.

The hydrostatic pressure from the right auricular reference level to the venipuncture site was determined by means of a spirit level and a metal tape. The reference level of Lyons, Kennedy, and Burvell<sup>8</sup> of 10 cm. from the surface of the examination table was used. The uncorrected manometer reading minus the hydrostatic pressure yielded the corrected venous pressure.

2. *General Procedure for the Study of the Effect of Postural Changes on Venous Pressure.* The Moritz and von Tabora manometer with a saline-filled system was used<sup>9</sup>. This instrument was chosen because of the difficulty encountered from clotting in repeat measurements with the phlebomanometer of Burch and Sodeman. The subjects were allowed to rest for 15 minutes before the initial measurements. The zero point on the manometer was set on a level with the phlebostatic axis of Winsor and Burch, or the hydrostatic pressure was measured and venous pressure corrected accordingly. The venipuncture site was on the level with the reference point for the heart or below this level. The arm was abducted to an angle between 45° and 60° and supported to prevent development of muscle tension. Special attention was given to the comfort of the patient in order to minimize the influence of muscle tension. Unless otherwise stated, 5 to 10 minutes were allowed after a change in body posture before venous pressure readings were

taken. Measurements were made over a period of 5 to 10 minutes, and the average of at least 3 readings was recorded.

3. *Reliability of Repeated Observations.* Supine values of venous tension were compared before and after tilting the patient to a 45° position. The venous pressure measurements used in the reliability analysis were obtained from data from the study of the effect of tilting (Part 5).

4. *Effect of Posture on Venous Pressure.* A. Comparison of Venous Pressure in Supine with Sitting Positions. The subjects were allowed to rest for 15 minutes in a 45° sitting position before venous pressure was measured. Measurements were then made in the initial 45° sitting position, a supine position, and again in a 45° sitting and a supine posture. The 10 individuals studied included both normal subjects and patients with chronic disease. This experiment was performed with the subject in a bed.

B. Serial Measurements of Venous Pressure with Changes in Body Position. Venous tension was determined at 1 to 3 minute intervals in (a) a supine position, (b) after assuming a 45° sitting position, and (c) after resuming the supine posture in 10 normal subjects.

In this experiment, and all subsequent ones except in sections 6 and 8, venous pressure measurements were made with the subject on a tilt table. The tilt table was so constructed that the head end could be raised to a 30°, 45°, 60°, or 90° angle (bending the patient at the hips), or the entire table could be tilted from the horizontal position to the same angles.

C. Venous Pressure in the Supine Position and in the 45° Sitting Position Before and After Resting 30 Minutes. Venous pressure measurements were repeated on a subsequent day on 8 of the 10 subjects on whom the serial measurements were made. After supine readings were obtained, venous pressure was measured in a 45° sitting position. The needle was removed from the vein and the patient was allowed to remain for 30 to 45 minutes in a 45° sitting position. Following this rest period, the needle was replaced in the same vein, and venous pressure was again measured.

5. *Effect on Venous Pressure of Bending as Compared with Tilting.* With use of the tilt table, bending of the patient was compared with tilting. Venous pressure was measured in the following successive positions: (a) supine, (b) with the head end of the tilt board raised to a 45° angle, (c) supine, (d) tilted to a 30° angle, (e) tilted to a 45° angle, and (f) supine. The 20 subjects used in this experiment consisted of normal indi-

viduals and patients in whom treatment with penicillin for primary and secondary syphilis was nearing completion.

6. *Factors Involved in the Rise of Venous Pressure.* An attempt was made to change the anatomical relation of surrounding structures to the subclavian and axillary veins. This was accomplished by passively supporting each shoulder so that the clavicle was displaced anteriorly and superiorly. The head was turned toward and away from the side of the measurement in an effort to decrease venous pressure. Ten individuals including normal subjects and patients with chronic disease were studied.

The effect of changes in posture on 4 patients with an abnormally high supine venous pressure (above 200 mm. saline) was studied. Three of the patients were in congestive heart failure; the other patient had a superior vena caval obstruction.

7. *The Relation Between Commonly Used Reference Points.* The effect of postural changes on venous pressure as well as the interpretation of venous pressure as an estimate of right auricular pressure is dependent upon the reference level used. Consequently, it is important to determine the relation of different reference levels to one another. Anthropometric measurements were made on the 20 subjects presented in Part 5 to determine the reference levels of Burch and associates<sup>10</sup>, Lyons, Kennedy and Burwell<sup>8</sup>, Moritz and von Tabora<sup>9</sup>, von Recklinghausen<sup>12</sup>, and Eyster<sup>4</sup>. For comparison, the reference levels were related to the surface of the examination table.

8. *Changes in Right Auricular Pressure with Changes in Posture.* Right auricular pressure was measured in 2 normal subjects. In one case, a saline manometer attached to an indwelling intracardiac catheter was used to

measure intracardiac pressure. In the other case, right auricular pressure was measured with the saline manometer and then with a Hamilton manometer<sup>5</sup>. The zero point on the saline manometer was set on a level with the phlebostatic axis. Saline was allowed to run into the right auricle until equilibrium was reached. Measurements with the Hamilton manometer were also referred to the phlebostatic axis.

**Results.** 1. *Comparison of Manometers.* The venous pressure in the normal subjects and in patients with disease but without a pathological basis for venous hypertension ranged from 33 to 159 mm. of water with the phlebomanometer of Burch and Sodeman and from 49 to 163 mm. of saline with the apparatus of Moritz and von Tabora. The tension in the veins of patients with congestive heart failure varied from 71 to 345 mm. of water with the instrument of Burch and Sodeman and from 69 to 337 mm. of saline with the second method. Calculation of the mean venous pressure showed a value of 111 mm. of water by the method of Burch and Sodeman, and 113 mm. of saline by the method of Moritz and von Tabora. This difference was not statistically significant ( $t = 1.35$ ;  $P = 0.8-0.9$ ;  $N = 31^*$ ).

2. *Reliability of Repeated Observations.* Supine measurements of venous pressure did not vary signifi-

\* The significance of the differences between positions were evaluated by calculating  $t$  values according to the formula:

$$t = \frac{\frac{\sum (x_1 - x_2)}{N}}{\sigma_{Mn \text{ diff.}}} = \frac{Mn \text{ diff.}}{\sigma_{Mn \text{ diff.}}}$$

$$\sigma_{Mn \text{ diff.}} = \frac{\sigma_{\text{diff.}}}{\sqrt{N - 1}}$$

$$\sigma_{\text{diff.}} = \sqrt{\frac{\sum (x_1 - x_2)^2}{N} - \left( \frac{\sum (x_1 - x_2)}{N} \right)^2}$$

where  $x_1$  and  $x_2$  are observations made before and after change in position.

cantly between repeated observations on the same patient before and after tilting to an angle of  $45^\circ$  (Fig. 3). The mean before tilting was 93 mm.; after tilting the mean was 95 mm. ( $t = 1.15$ ;  $P = > 0.9$ ;  $N = 20$ ). The correlation between measurements made before and after tilting was 0.9 ( $N = 20$ ).

3. *Effect of Posture on Venous Pressure.* A. Comparison of Venous Pres-

were  $155 \pm 22$ ,  $109 \pm 17$ ,  $145 \pm 21$ , and  $110 \pm 20$  mm. of saline respectively (Fig. 1). The difference between mean  $45^\circ$  and mean supine readings was 41 mm. ( $t = 4.58$ ;  $P = < 0.01$ ;  $N = 10$ ).

B. Serial measurements of Venous Tension with Changes in Body Position. When the patient assumed a  $45^\circ$  sitting position from a supine posture, the mean venous pressure increased

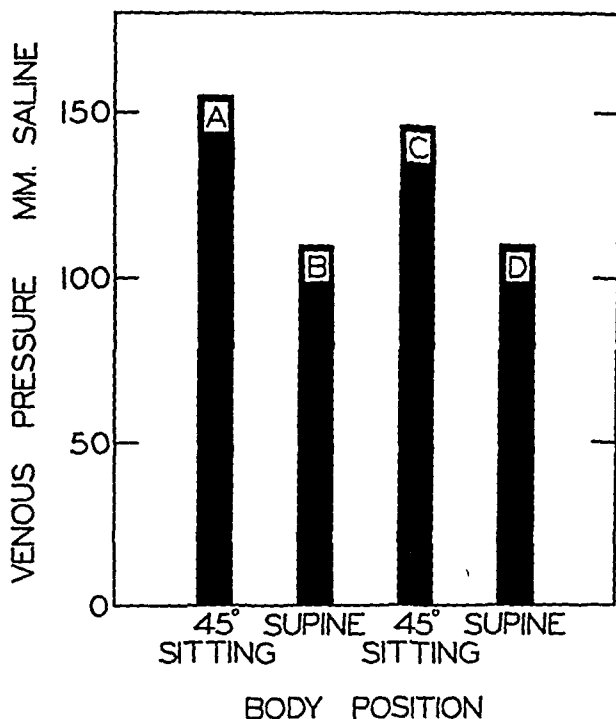


FIG. 1. The effect on venous pressure of changing body position from a  $45^\circ$  sitting posture to a supine position. Mean values for 10 subjects. Measurements: A,  $45^\circ$  sitting posture after 15 minutes rest in this position. B, supine position. C,  $45^\circ$  sitting position. D, supine position.

sure in Supine with Sitting Posture. Elevated venous pressure was observed in a sitting posture regardless of whether the patient rested for 15 minutes in a sitting position or was changed to a sitting posture after the supine measurements were made. Mean venous pressure in 4 successive positions (in a  $45^\circ$  sitting, supine,  $45^\circ$  sitting, and supine) for 10 patients

from  $87 \pm 10$  to  $145 \pm 18$  mm. of saline ( $t = 6.93$ ;  $P = < 0.01$ ;  $N = 10$ ) (Table 1). This increase was followed by a slight drop in venous tension in some cases (see Case J. C., Fig. 3), but the pressure levelled off within a 15 to 20 minute period and remained significantly higher than the supine values. In one case only (Case J. G., Fig. 2), venous pressure remained con-

stant with the change in body posture. When the subjects were returned to the supine position, the mean pressure dropped from  $145 \pm 18$  mm. to  $82 \pm 10$  mm. ( $t = 8.44$ ;  $P = 0.01$ ;  $N = 10$ ). The final pressure recorded was not significantly different from the original supine values ( $t = 1.76$ ;  $P = 0.8-0.9$ ;  $N = 10$ ).

C. Venous Pressure in the Supine Position and in the  $45^\circ$  Sitting Position Before and After Resting for 30

value of  $91 \pm 13$  to  $142 \pm 22$  mm. of saline ( $t = 3.90$ ;  $P = < 0.01$ ;  $N = 8$ ) for the sitting posture. After 30 minutes, the mean venous pressure for the  $45^\circ$  sitting position was  $150 \pm 24$  mm., which did not differ significantly from the mean value obtained before the rest period, ( $t = 1.78$ ;  $P = 0.8-0.9$ ;  $N = 8$ ).

4. *Effect on Venous Pressure of Bending as Compared with Tilting.* The average venous pressures in the

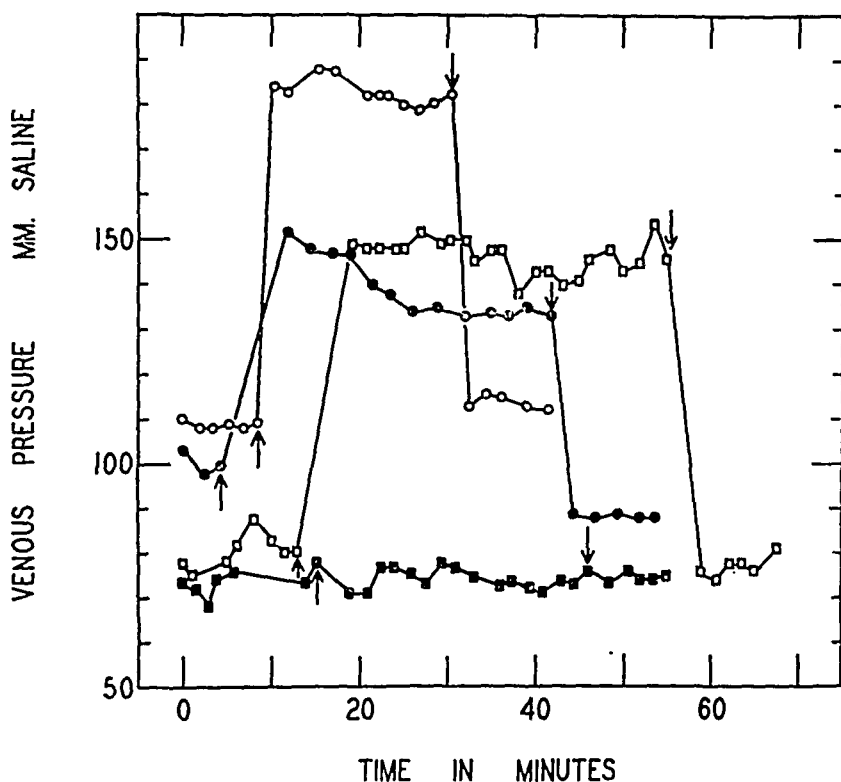


FIG. 2. Serial venous pressure measurements (mm. saline) in supine and in the  $45^\circ$  sitting position in 4 subjects. Arrows indicate change in posture:

↑ supine to  $45^\circ$  sitting ↓  $45^\circ$  sitting to supine

|       |               |
|-------|---------------|
| ○ ○ ○ | Subject C. W. |
| ● ● ● | " J. C.       |
| □ □ □ | " J. H.       |
| ■ ■ ■ | " J. G.       |

Minutes. With the exception of one case (Case J. C.), an increase in venous pressure occurred with the assumption of the  $45^\circ$  sitting position in the same subjects that venous tension became elevated during the serial measurements (Table 1). Venous pressure increased from a mean supine

supine,  $45^\circ$  sitting position, supine, tilted to a  $30^\circ$  angle, tilted to a  $45^\circ$  angle, and supine positions were  $95 \pm 7$ ,  $145 \pm 9$ ,  $93 \pm 7$ ,  $113 \pm 9$ ,  $140 \pm 10$ ,  $95 \pm 7$  mm. of saline respectively (Fig. 3). When the results of the entire group were considered, both bending and tilting the patient resulted in a

significant elevation in venous pressure (Bending,  $t = 9.03$ ;  $P = 0.01$ ;  $N = 20$ ; tilting,  $t = 8.51$ ;  $P = 0.01$ ;  $N = 20$ ). However, in 4 cases of this group, the tension remained constant. The difference between bending and tilting was insignificant ( $t = 1.34$ ;  $P = 0.8-0.9$ ;  $N = 20$ ).

5. *Factors Involved in the Rise of Venous Pressure.* The displacement of the clavicle anteriorly and superiorly by supporting the shoulder resulted in a slight increase in venous pressure

the tension approach the supine value. When the head was turned away from the side of the measurement, venous pressure increased slightly.

In 4 cases, the venous pressure in the supine position was above 200 mm. of saline. In these patients, venous tension remained constant as the position of the body was changed from supine to a partially erect posture. One of the 3 patients with heart failure was studied again after cardiac compensation had been accomplished and

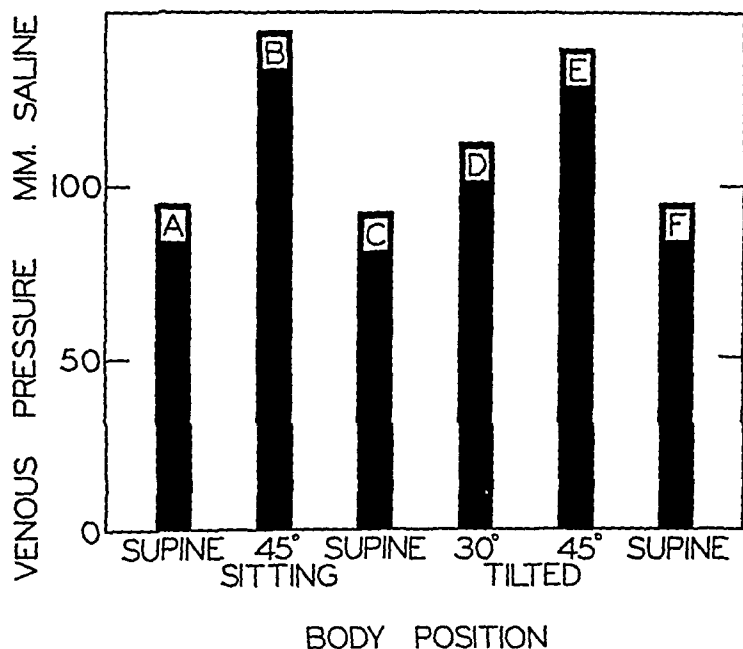


FIG. 3. The effect on venous pressure of bending as compared with tilting the subject. Mean values for 20 subjects. Measurements in: A, supine position after 15 minutes rest. B, after raising subject to 45° sitting position by bending at hips. C, after return to supine position. D, after tilting entire body to 30°. E, after changing body position from 30° to 45° by tilting. F, after returning to horizontal position.

in most cases. This rise in venous pressure occurred regardless of whether the same or contra-lateral shoulder was moved anteriorly.

Turning of the head toward the side of measurement often resulted in a slight reduction in venous tension (10 to 20 mm.), but in no case did

a normal supine venous pressure was present. This patient then showed the usual increase in venous pressure with the assumption of a 45° sitting posture.

6. *Relation of Commonly Used Reference Points to One Another.* The results of anthropometric measurements made to determine differences

between various reference levels are presented in Table 2. The greatest difference between reference levels was 79 mm.; that is, between the reference point of 10 cm. above the examination table and the reference point of Moritz and von Tabora. The latter point is usually on a level with the right auricle (radiological evidence<sup>8</sup>), but a negative venous pressure was recorded several times during this investigation with this reference level.

7. *Changes in Right Auricular Pressure with Changes in Position.* Right auricular pressure decreased in each of 2 subjects with a change in body position from a supine position to a 45° sitting posture. In the case in which the measurements were made with the saline manometer only, right auricular pressure decreased from 105 to 55 mm. of saline. In the other case, right auricular pressure decreased from 120 to 60 mm. of water and the results

TABLE 1. VENOUS PRESSURE IN THE SUPINE AND THE 45° SITTING POSITION ON 2 DIFFERENT DAYS

| Subjects       | Day One                             |              | Day Two   |        |              |                                    |
|----------------|-------------------------------------|--------------|---|--------|--------------|------------------------------------|
|                | Serial Venous Pressure Measurements |              | Venous Pressure Before and After Resting for 30 Minutes |        |              |                                    |
|                | Supine*                             | 45° Sitting† | Supine*   | Supine | 45° Sitting† | 45° Sitting Position after 30 Min. |
| 1. C.W.        | 109                                 | 184          | 114   | 100    | 178          | 189                                |
| 2. J.C.        | 100                                 | 152          | 88  | 102    | 107          | 116                                |
| 3. J.M.        | 92                                  | 128          | 82  | 101    | 153          | 161                                |
| 4. E.H.        | 87                                  | 157          | 69  | 88     | 115          | 146                                |
| 5. H.E.        | 85                                  | 141          | 84  | —      | —            | —                                  |
| 6. N.C.        | 84                                  | 147          | 76  | 83     | 167          | 159                                |
| 7. E.H.        | 75                                  | 137          | 75  | —      | —            | —                                  |
| 8. C.W.        | 80                                  | 184          | 85  | 85     | 181          | 178                                |
| 9. J.H.        | 80                                  | 149          | 77  | 69     | 137          | 151                                |
| 10. J.G.       | 74                                  | 75           | 74  | 100    | 98           | 97                                 |
| Mean Pressure  | 86.6                                | 144.7        | 82.4  | 91.0   | 142.0        | 149.6                              |
| Mean Variation | 9.7                                 | 18.1         | 9.5   | 12.8   | 22.2         | 23.8                               |

\* Average value of supine measurements.

† Initial reading 2 to 5 minutes after assuming the 45° position.

§ All venous pressure measurements in mm. saline.

TABLE 2. MEAN VALUES OF ANTHROPOMETRIC MEASUREMENTS OF REFERENCE LEVELS ON 20 SUBJECTS

| Reference Level               | Definition  | Distance in mm. above examination table at level of 4th costochondral junction |
|-------------------------------|---|--|
| 1. Lyons, Kennedy and Burwell | 100 mm. above surface of examination table                    | 100  |
| 2. von Recklinghausen         | Midpoint of thorax  | 110  |
| 3. Winsor and Burch           | Phlebostatic axis is the line of intersection of two planes.* | 114  |
| 4. Moritz and von Tabora      | 50 mm. dorsal to the 4th costochondral junction               | 179  |
| 5. Eyster                     | Junction of anterior and middle thirds of thoracic diameter   | 146  |

\* A frontal plane  $\frac{1}{2}$  the thoracic diameter at the level of the base of the xiphoid process of the sternum intersects a cross sectional plane at the level of the 4th intercostal space adjacent to the sternum.



obtained with the 2 manometers did not vary significantly.

**Discussion.** The experiments performed in this investigation demonstrate an increase in antecubital venous pressure with a change in body position from a supine to an erect posture. This finding differs from the results obtained by Burch and associates who reported no change in venous pressure with postural changes. The difference in the results reported in this paper and those reported by Burch and his co-workers cannot be due to the use of a different reference level because the venous pressure measurements in this investigation were referred to the phlebostatic axis of their study. Neither can the differences be ascribed to the type of manometer used, since it was shown that the phlebomanometer of Burch and Sodeman and the saline manometer of Moritz and von Tabora gave equivalent values. To eliminate the influence of the type of bed on the measurements (with a possible alteration in the pressure relations of surrounding structures to the vein), both a hospital bed and a padded table were used. Regardless of the type of bed used for each experiment, the venous pressure was elevated in sitting positions.

The elevated venous pressure present in sitting positions was not the result of failure to allow sufficient time for cardiovascular adjustment after a change in posture. This statement is supported by evidence obtained from the serial measurements of venous pressure. Venous tension was elevated after 20 minutes of repeated observations (Fig. 2). The slight decrease in venous pressure which occurred during the first few readings in the 45° sitting position, in some cases, is probably the result of relaxation.

In order to eliminate the effect that continuous infusion of saline might exert on venous tension (Serial Meas-

urements), venous pressure was determined before and after resting for 30 minutes in the 45° sitting position. The results of this experiment furnish additional evidence that venous pressure remains elevated in the sitting posture and that sufficient time was allowed for cardiovascular adjustment.

Is the elevated venous pressure in the sitting position the result of pressure from surrounding structures on the axillary or subclavian vein? To answer this question, studies of venous pressure were made before and after tilting the patient to a 45° position. By tilting the patient, the anatomical relation of structures remained unchanged in different body positions except as it might be affected by gravity. The finding that the tilting as well as the bending of the patient resulted in an elevation of venous pressure indicates that local pressure on the vein from surrounding structures is not the causative factor. Attempts to alter the anatomical relation of structures to the large veins by turning the head or by displacing the clavicle resulted in an increase or failed to demonstrate a fall in venous pressure of sufficient magnitude to be significant. This finding also indicates that pressure from surrounding structures on the axillary and subclavian vein is not responsible for the elevated venous pressure in the sitting position.

Assuming that measurements of venous pressure in an antecubital vein was indicative of right auricular pressure, it would be expected that right auricular pressure would increase with a change from a supine to a sitting position. On the contrary, a decrease in right auricular pressure occurred with this change in position. The decrease in right auricular pressure may have been the result of the shifting of blood from superior to inferior portions of the body due to gravity.

Presumably, venous tension could be

evaluated in the sitting posture by determining the normal range of venous pressure in various sitting positions. However, the validity of such measurements seems questionable since 4 normal subjects failed to show an elevated tension in the sitting posture. Furthermore, venous pressure remained constant upon assumption of a 45° sitting position in all 4 patients with a supine venous tension greater than 200 mm. of saline. This result suggests that the mechanism responsible for the elevation of venous pressure in sitting positions does not operate at high levels of venous pressure. Consequently, no attempt was made to establish the normal range in different sitting positions.

When the reference point of Moritz and von Tabora was used, a negative venous pressure was recorded several times. This finding indicates that this reference level is unsatisfactory for venous pressure measurements. The reference levels of von Recklinghausen, of Lyons, Kennedy, and Burwell, and of Winsor and Burch did not vary greatly from each other in 20 patients, and each level resulted in positive venous pressure readings. From the available data it cannot be stated which one of these reference points is most valid. However, it should be pointed out that any reference level which is located by determining the anterior-posterior diameter of the chest will yield a low venous pressure in patients with a high thoracic diameter. In view of this, it seems that the reference level of Lyons, Kennedy, and Burwell of 10 cm. from the examination table is the most practical one to use.

**Summary and Conclusions.** 1. Comparison of the phlebomanometer of Burch and Sodeman with the saline

manometer of Moritz and von Tabora revealed no significant difference in the values obtained for venous pressure.

2. When the phlebostatic axis of Winsor and Burch was used as a reference level, venous pressure increased as the patient changed posture from a supine to a sitting position.

3. Tilting the patient to a 45° angle resulted in an increase in venous pressure which was not significantly different from the increase which occurred when the patient assumed a 45° sitting position.

4. The elevated venous tension present in sitting positions was not lowered by altering the anatomical relation of surrounding structures to the axillary and subclavian veins.

5. The available data do not allow a conclusion to be made as to the mechanism for the observed increase in venous pressure. It is suggested that the high venous pressure found in sitting positions was not the result of the pressure of surrounding structures on the proximal veins.

6. Right auricular pressure decreased in each of 2 subjects with a change from the supine to a 45° sitting position. It is suggested that this fall in intracardiac pressure is the result of a shift in blood from superior to inferior parts of the body by gravity.

7. Failure of venous pressure to rise with the assumption of the sitting posture in some patients precludes the establishment of normal standards in various sitting positions.

8. It cannot be definitely stated which one of the commonly used reference levels for venous pressure is most valid, but it is suggested that the level of 10 cm. above the examination table is generally the most feasible.

We are indebted to Mrs. Elizabeth Strawn, R.N., for technical assistance with the venous pressure measurements and to Dr. James Birren for suggestions concerning the statistical treatment of the data.

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# RENAL STUDIES IN ACUTE INFECTIOUS (EPIDEMIC) HEPATITIS\*

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In the course of study of infectious (epidemic) and homologous serum hepatitis induced in human volunteers, it was observed that during the pre-icteric stage bilirubin frequently was detected in the urine before measurable increases in total or prompt direct reacting serum bilirubin occurred<sup>11,13</sup>. On the other hand, in the convalescent stage of hepatitis, bilirubin often disappeared from the urine while the total and prompt direct reacting serum bilirubin concentrations still were significantly elevated. Thus in hepatitis the presence or absence of bilirubinuria did not appear to be entirely related to the concentration of serum bilirubin. Possible explanations for this phenomenon include: 1, a qualitative difference in the type of bilirubin present at different stages of hepatitis or in its availability to the kidney for excretion; 2, a change in the functional capacity of the kidneys to excrete bilirubin during the different stages of hepatitis. The frequent occurrence of renal disturbance in hepatic disease suggested an investigation of the second possibility. The present report is an explorative survey of renal function during the course of acute infectious (epidemic) hepatitis.

**Methods of Study. Subjects.** The renal studies were carried out during the course of other investigations of infectious hepatitis (I H virus). Material containing the I H virus was given orally to 6 white male volunteers<sup>12</sup>. Studies of liver and kidney function were made frequently before, during and after the onset of the disease. The men ranged in age from 18 to 24 years, and none had any clinical or laboratory evidence suggestive of hepatic

or renal disturbances prior to the onset of the induced hepatitis. One, J. B., age 25, however, subsequently recalled an illness suggestive of acute glomerulonephritis at the age of 11 years. This illness apparently was followed by a complete clinical recovery within a few weeks.

Of the 6 men inoculated with the I H virus, 4 developed hepatitis after incubation ranging from 18 to 27 days. In 3, the illness was moderately severe with jaundice, while in the 4th, M.T., it was mild, the jaundice not being apparent.

**Procedure.** Addis counts and urea clearance determinations were made once weekly on each man except during the 1st week of illness, when studies were done twice. They were begun before inoculation of the virus and continued for 2 to 3 months after the onset of hepatitis. Liver function tests including serum and urine bilirubin determinations were performed twice weekly.

**Addis Count<sup>1</sup>.** The subjects ingested no liquids during the 24 hour test period. All urine excreted during the second 12 hours was collected and examined promptly for: *a*, 12 hour urine volume, *b*, specific gravity, *c*, total protein<sup>14</sup>, *d*, total erythrocyte count, *e*, total leukocyte count, and *f*, total cast count. The values generally accepted as normal and the pre-hepatitis values of these men are given in Table 1. Although the results of the Addis counts done prior to the onset of hepatitis in these volunteers were within the normal range, their own pre-hepatitis values probably provide a better means for evaluating the effect of hepatitis. It should be noted that the erythrocyte and cast excretion are plotted on logarithmic scales on the charts.

**Urea Clearance.** Urea nitrogen was measured in the same urine specimen used for the Addis count and in blood drawn at some time during the urine collection period. The urea clearance was calculated according to the formula of Möller, McIntosh, and Van Slyke<sup>9</sup>: *U* is the urine urea nitrogen, *B* is the

$$\text{Blood in ml. cleared of urea per minute} = \frac{U}{B} \sqrt{V}$$

blood urea nitrogen, and *V* is the volume of

\* Conducted in part under The Commission on Liver Disease, Army Epidemiological Board.

urine in ml. excreted per minute. This formula, which gives the "standard" urea clearance, was selected because the urine flow was less than 1.5 ml. per minute in all instances<sup>15</sup>. The normal mean is 54 ml. of blood cleared of urea per minute, and the normal range is from 40 to 69 ml.<sup>15</sup>.

*Bilirubin Determinations.* Serum bilirubin

was measured according to methods previously described<sup>10</sup>. The normal range for total serum bilirubin is 0.1 to 1.0 mg. per 100 ml., and for prompt direct reacting bilirubin 0.1 to 0.21 mg. per 100 ml. The Harrison spot test<sup>5</sup> was used to measure urine bilirubin, and readings of plus 2 or greater were judged to be abnormal.

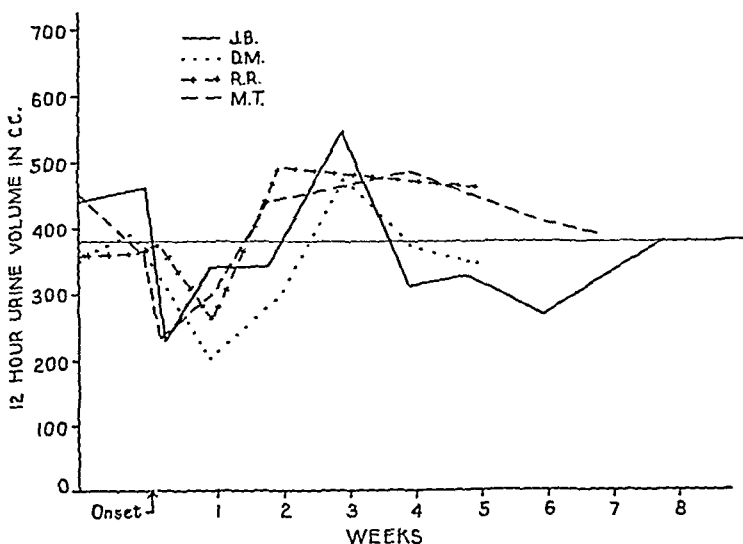


FIG. 1. Twelve hour urine volumes. These fell below pre-hepatitis levels in all 4 men during the first 10 days of hepatitis. The normal mean established by Addis is 380 ml. In this and subsequent figures, the vertical arrow at the bottom of the chart indicates the onset of the hepatitis.

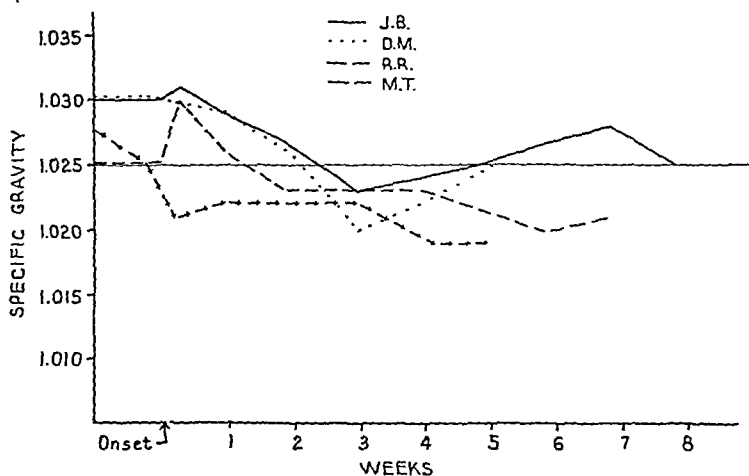


FIG. 2. Urine specific gravity. That of M.T. varied inversely with his urine volume throughout the course of his very mild hepatitis. Those of the other 3, who had moderately severe hepatitis, fell below pre-hepatitis levels during the first 10 days of illness at a time when the urine volumes were also decreased. The minimal normal specific gravity during fluid restriction for an Addis count is 1.025.

**Results. 12 Hour Urine Volume.** Figure 1 shows that the 12 hour urine volumes dropped rather sharply during the 1st week of hepatitis, then gradually increased until, in the 3rd week, they were above the normal mean. The urine volumes remained elevated during the 4th and 5th weeks before returning toward the normal mean.

**Specific Gravity.** In 3 of the 4 subjects, the urine specific gravity decreased during the 1st week of hepatitis. The man who had the mildest hepatitis, M. T., did not show this change until the 2nd week. The specific gravity readings were low on 2 of the

the generally accepted upper limit of normal. M. T.'s mild attack caused only a slight increase over pre-hepatitis values. The increased protein excretion did not persist longer than 3 weeks in any of the 4 men.

**Total Erythrocyte Count.** Two men excreted red blood cells in excess of the maximal normal, the increase being very great in one. The others showed an increased number of erythrocytes in their urine as compared to their pre-hepatitis levels, but the values found remained within the generally accepted normal limits. A marked increase in red blood cell excretion occurred in the

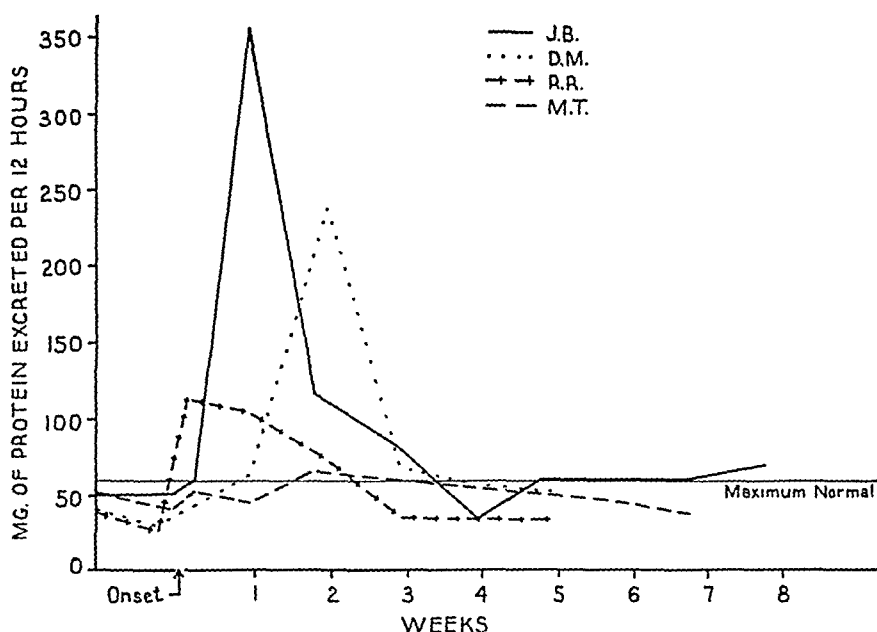


FIG. 3. Abnormal proteinuria. This occurred at the onset of hepatitis in all 4 men. The mild illness of M.T. caused only a slight increase over his pre-hepatitis level.

men for 2 weeks, and remained low on the other 2 at the end of 6 weeks.

For the most part, the specific gravity readings and 12 hour urine volumes varied inversely as would be expected. However, at the onset of hepatitis the specific gravity as well as the urine volume decreased in 3 of the 4 men.

**Total Protein.** All 4 men had an increase in the amount of protein in the urine. In 3, the increase exceeded

urine of J. B., age 25 years. This man had the history suggestive of renal disease at the age of 11.

The increase in erythrocytes began during the 1st week of hepatitis in all 4 men. The onset of hepatitis and hematuria occurred simultaneously in J. B., whose illness began during a collection period for an Addis count. This early study showed an abnormally large number of red blood cells in the

urine. Erythrocyte excretion was within limits considered normal in 3 men at the end of 1 month, but remained elevated for 2 months in the case of J. B. At the end of 3 months, J. B. also had returned to normal (not shown on the figure).

**Total Leukocyte Count.** No significant increase in the number of leukocytes was observed in the urine of any of these men during this study. For this reason, these results have not been charted.

none had an increased number of casts prior to the onset of hepatitis, these findings are probably significant.

**Urea Clearance.** The urea clearance determinations reveal a trend toward reduced urea elimination early in hepatitis. D. M. had a significant elevation of blood urea nitrogen which rose from 18 to 26 mg. per 100 ml. during the 1st week of illness, then returned to normal in the 2nd week. The results are inconclusive and hence are not shown.

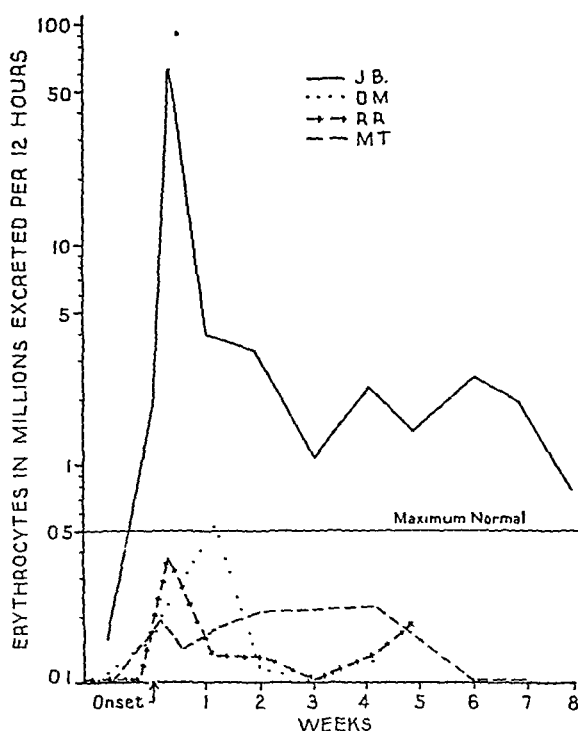


FIG. 4. Erythrocyte excretion. All 4 men had an increased erythrocyte excretion over pre-hepatitis values, the increase being over the maximal normal in 2. J.B., with the history suggestive of renal disease in childhood, had a tremendous increase in red blood cell excretion.

**Total Cast Count.** Abnormally increased cast excretion occurred in all 4 men at some time during the hepatitis. Granular casts predominated with occasional hyaline casts being seen. No other types were found. Cast excretion was somewhat irregular and not uniform in the 4 men, but since

**Serum and Urine Bilirubin.** The total serum bilirubin rose to about 10 mg. per 100 ml. in 3 men. In the 4th, it increased from normal pre-hepatitis values to about 1.5 mg. per 100 ml., returning within 3 weeks to the previous level. The prompt direct reacting bilirubin values were roughly

one-half the total serum bilirubin levels, and closely paralleled them throughout the course of the hepatitis in all 4 men.

The urine of each man contained abnormally large amounts of bilirubin from 1 to 4 days before the total or prompt direct reacting serum bilirubin increased significantly. It is also interesting that the urine was free of abnormal amounts of bilirubin for approximately 1 to 3 weeks before the serum bilirubin fell to normal.

Elsom<sup>3</sup> studied by Addis counts the renal function of 16 patients with obstructive jaundice and 1 with arsenical hepatitis. An increased excretion of casts was the most striking abnormality noted, although an increased number of epithelial cells and leukocytes was equally consistent. The low incidence of albuminuria found by Elsom was not substantiated by Thompson, Frazier, and Ravdin<sup>17</sup> who found at least a trace of albumin in the urine specimens of all patients

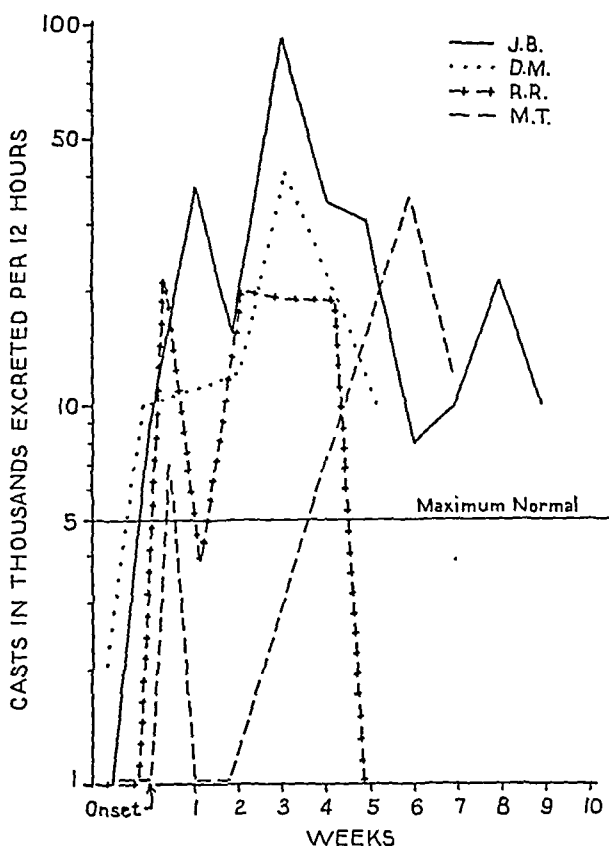


FIG. 5. Cast excretion. From normal pre-hepatitis values cast excretion increased greatly during the hepatitis in all 4 subjects. The increases were above the maximal normal.

**Discussion.** We had the advantage in this study of being able to perform renal function tests prior to the onset of hepatitis and for 2 to 3 months after the onset. Furthermore, the etiological agent responsible for the hepatitis was definitely known<sup>12</sup>, the disease having been artificially induced and uniform in all 4 subjects.

with obstructive jaundice. These investigators noted also a reduced concentrating power of the kidneys in 22 of the 32 patients with obstructive jaundice, and in 43 of 61 patients who eventually died of hepatic or biliary tract disease. Of the 32 patients with obstructive jaundice, leukocytes were found in abnormal numbers in 17,



casts in 13, and red blood cells appeared sporadically in 4.

The present study reveals a definite reduction in the concentrating power of the kidneys early in the course of hepatitis in 3 of the 4 subjects. The concentrating power of the kidneys is generally accepted as a measure of the functional capacity of the renal tubules<sup>4</sup>.

The appearance of increased amounts of protein in the urine suggests the presence of some factor producing renal (presumably glomerular) irritation. An increase of bile salts in the blood has been suggested in the work of Stewart and Cantarow<sup>16</sup> as the cause of the renal irritation. Hepatic nephrotoxins have been proposed by Helwig and Schutz<sup>5</sup> and

thymol turbidity<sup>10</sup>—were abnormal during this early phase of hepatitis, suggesting the presence of hepatic injury. Injured hepatic cells may have been producing nephrotoxins; the relationship of renal disturbance to hepatic damage, however, is uncertain.

Increased numbers of red blood cells in the urine occurred to some degree in all 4 subjects early in the course of hepatitis. This finding was not characteristic of cases of "cholemic nephrosis", as reported by Elsom<sup>3</sup> and by Thompson, Frazier, and Ravdin<sup>17</sup>. This suggests that the glomeruli may be more prominently involved in viral hepatitis than in cholemic nephrosis secondary to obstructive jaundice. It is of interest that the subject who displayed the greatest increase of red

TABLE 1. ADDIS COUNTS.

|                                   | Normal range<br>(according to Addis) | Pre-hepatitis range<br>for these subjects <sup>a</sup> |
|-----------------------------------|--------------------------------------|--|
| (1) 12 hr. urine volume           | 380 ml. $\pm$                        | 350 — 460 ml.  |
| (2) Specific gravity              | 1.025 or over                        | 1.025 — 1.031  |
| (3) Total protein / 12 hr.        | 0 — 60 mg.                           | 25 — 50 mg.  |
| (4) Total RBC excretion / 12 hr.  | 0 — 500,000                          | 0 — 100,000  |
| (5) Total WBC excretion / 12 hr.  | 0 — 2,000,000                        | 0 — 1,400,000  |
| (6) Total cast excretion / 12 hr. | 0 — 5,000                            | 0 — 2,000  |

<sup>a</sup> Based on 11 Addis counts done on 6 men.

Boyce and McFetridge<sup>2</sup>. It is to be noted in the present study that the appearance of increased protein in the urine corresponded closely with the appearance of bilirubinuria. Retained biliary products may have caused the renal irritation and proteinuria, or proteinuria induced by hepatic nephrotoxins may have carried bound bilirubin into the urine. Bilirubinuria occurring before any detectable rise in the total or prompt direct reacting serum bilirubin in early hepatitis supports the latter hypothesis. It is possible, of course, that the virus itself affected the kidney directly. Certain liver function tests—cephalin-cholesterol flocculation, colloidal gold, and

blood cells in the urine had a history suggestive of acute glomerulonephritis 14 years previously. It is impossible to know whether this hematuria was due to a reactivated glomerulonephritis, renal involvement associated with hepatitis in a man with previously damaged kidneys, or simply renal involvement associated with hepatitis in itself. The prompt improvement following recovery from hepatitis suggests that this was not a reactivation of glomerulonephritis.

The appearance of increased numbers of casts in the urine of all 4 men, as well as red blood cells and protein, further supports the hypothesis that renal irritation occurs in early

infectious (epidemic) hepatitis. The large numbers of epithelial cells and leukocytes in the patients with obstructive jaundice reported by Elsom<sup>3</sup> were not found in these men with hepatitis.

The urea clearance determinations reveal a trend toward reduced clearance early in hepatitis. Numerous workers, among whom are Meyers and co-workers<sup>8</sup>, Wilensky<sup>18</sup>, and Lichtman and Sohval<sup>7</sup>, have reported the relation of liver and biliary tract disease to renal damage with nitrogen retention.

The findings indicate that viral hepatitis is accompanied by a demonstrable change in renal function, and that a more detailed study by methods permitting evaluation of glomerular and tubular activities separately is desirable. This disturbance of renal function

is probably not specific for acute infectious hepatitis, and may be found in other diseases.

**Summary.** An exploratory survey of changes in renal function during the complete course of infectious hepatitis (I H virus) induced in 4 volunteers is presented. Addis counts and urea clearance determinations were used in this survey, which was done in conjunction with a study of liver function.

The following changes in renal function were observed early in the course of acute infectious hepatitis: 1, decrease in the concentrating power of the kidneys; 2, increase in protein, erythrocytes, and casts excreted in the urine; and, 3, trend toward reduced urea clearance early in hepatitis.

I am indebted to Dr. J. R. Neefe and Dr. J. G. Reinhold, The Hospital of the University of Pennsylvania, for their assistance and guidance. I also want to thank Dr. Joseph Stokes, Jr. and Dr. T. F. McNair Scott, The Children's Hospital of Philadelphia, for their helpful suggestions in the preparation of this paper.

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# CLINICAL REPORT ON THE TOXICITY OF A NEW MERCURIAL DIURETIC (THIOMERIN) FOR SUBCUTANEOUS ADMINISTRATION

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ORGANIC compounds of mercury have been used extensively as diuretic agents since 1920<sup>8</sup>, particularly in the management of congestive heart failure. These have been effective, but a number of toxic reactions has resulted.

Over 30 immediate fatalities following injection of mercurial diuretic compounds have been reported since 1925. These have been well summarized by DeGraff and Nadler<sup>2</sup> in 1942 and by Wexler and Ellis<sup>11</sup> in 1944. Since then several more have been reported<sup>1,9</sup>. In all these cases the drugs were injected intravenously; fatalities have never been noted by the intramuscular route<sup>2,8</sup>. Severe non-fatal shock and collapse reactions have been more numerous and occur with all methods of administration<sup>2,8,11</sup>. Many reactions of less serious nature have been noted, such as hypersensitivity states (asthma, urticaria and fever)<sup>2,8,11</sup>, transient dyspnea, substernal oppression, and mild shock<sup>8</sup>. One case of tubular nephrosis due to acute mercury poisoning has been reported<sup>10</sup>.

The incidence of serious toxicity is low when compared with the large number of injections<sup>2,8,11</sup>, and even less frequent following intramuscular

injection. This has led some physicians to recommend the intramuscular route exclusively<sup>2,7,8</sup>. However, local pain and irritation is a frequent objection. No one of the common diuretics (mercuhydrin, salyrgan-theophylline and mercuzanthin) are free from local effects, but each has a group recommending it<sup>7</sup>.

Considerable effort has been directed toward developing a mercurial diuretic which is systemically less toxic and locally non-irritating and readily administered. Recently the disodium salt of N ( $\gamma$ -carboxymethylmercapto-mercuri- $\delta$ -methoxy) propyl camphoric acid (Thiomerin<sup>®</sup>) has been introduced for subcutaneous use. This compound shows chemical similarity to mercurphylline (mercuzanthin), but the theophylline has been replaced by sodium mercaptacetate with the formation of a mercaptide. Cardiac toxicity in experimental animals has been reported to be about 1/160 that of other mercurials given intravenously<sup>5</sup>. It is readily soluble in water, but because of instability in solution it is at present supplied in powder form with an ampule of distilled water. As now available this solution is stable

\* Supplied by Campbell Products, Inc., New York.

for 2 weeks or more at room temperature and if kept refrigerated will last for several months but should be discarded if color change or cloudiness develops.

**Method of Study.** This report presents the clinical experiences with Thiomerin, and deals specifically with local and systemic toxic effects.

Two groups were studied: a small hospitalized group of 59 patients in which careful observations were possible, and a larger

metastases from a gastric carcinoma and one had pulmonary emphysema.

Thiomerin was administered subcutaneously in doses of  $\frac{1}{2}$  to 3 cc., equivalent to 0.07 to 0.42 gm. of the compound, or 0.02 to 0.12 gm. of mercury. The most common dose was 1 cc., 2 cc. being next in frequency. The 59 hospitalized patients received a total of 430 injections, and the 350 out-patients a total of 1639 injections. The hospitalized patients received 1 to 35 injections at intervals of 1 to 3 days, the clinic patients 1 to 25 injections at intervals of 1 to 4 weeks, as determined by the response.

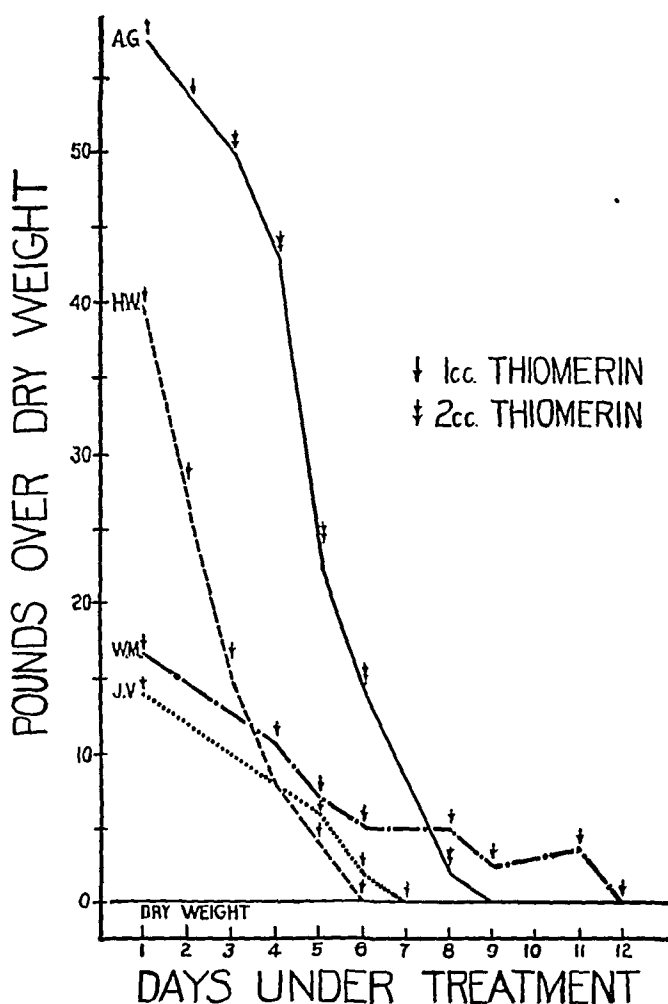


FIG. 1.—Weight Loss in 4 Patients Treated with Thiomerin.

group of 350 out-patients seen at intervals of 1 to 4 weeks. The clinic group consisted entirely of patients with various degrees of congestive heart failure. Forty-nine of the hospitalized group were in congestive heart failure, 4 had ascites and edema of the lower extremities due to hepatic cirrhosis, 4 were in the nephrotic stage of chronic glomerulonephritis, one had ascites due to peritoneal

**Results.** Results were evaluated by weight loss and clinical improvement. The achievement of "dry weight"<sup>4</sup> was used as a measure of effective diuresis. In the out-patient group diuresis was satisfactory. Dietary cooperation was found to be necessary for maintenance

of dry weight. In 56 of the 59 hospitalized patients the diuresis was equal to or better than that to be expected from other diuretic agents. Occasionally as much as 20 pounds of weight was lost in 24 hours by an excessively edematous patient. Typical responses of 4 of this group are indicated in Fig. 1.

Generalized toxic reactions have been absent, except for occasional development of muscle cramps, fatigue and weakness resulting from too rapid depletion of electrolyte and water. These symptoms were usually corrected by adjusting the frequency of administration and dose<sup>4</sup>, and adjusting the intake of water and electrolyte. No febrile reactions, hypersensitivity

it necessary to discontinue the administration of Thiomerin because of local discomfort or irritation. No evidence of kidney damage was observed (Table 1).

**Discussion.** Thiomerin administered by the subcutaneous route is an effective diuretic agent. The absence of all but minor local irritative phenomena, the apparent complete absence of systemic toxicity and the ease of administration provide a definite advantage. The incidence of excessive depletion of electrolyte and water is no greater than observed with other organic mercurial diuretic agents<sup>2,6,8,11</sup>.

Many patients in congestive heart failure require a maintenance dose of mercurial diuretics at varying inter-

TABLE 1.—SUMMARY OF EFFECTS OF 2069 DOSES OF THIOMERIN IN 409 PATIENTS

|                   | Number<br>Patients | Number<br>Injections | Good | Diuresis<br>Fair | Poor | Systemic <sup>o</sup><br>Reactions | Local <sup>oo</sup><br>Reactions |
|-------------------|--------------------|----------------------|------|------------------|------|------------------------------------|----------------------------------|
| Hospital Patients | 59                 | 430                  | 51   | 5                | 3    | 0                                  | 5                                |
| Clinic Patients   | 350                | 1639                 |      | ...              |      | 0                                  | 18                               |
| TOTAL             | 409                | 2069                 |      |                  |      | 0                                  | 23                               |

\* Nine deaths in hospitalized patients unassociated with Thiomerin.

\*\* In no case was it necessary to discontinue use of Thiomerin.

\*\*\* Diuresis was generally satisfactory. Patients were seen no oftener than once a week making evaluation of diuresis difficult.

states, gastrointestinal symptoms, or systemic reactions have been observed thus far.

Local, immediate and delayed irritative reactions occurred, but have been minimal. Transient burning and occasional pain following injection were noted in a few patients, at most lasting 15 to 30 minutes. Patients rarely complained of this and its presence was determined by questioning. A few patients developed local pain and small persistent nodules which were slightly tender for 1 or 2 days. Two instances of small, slightly tender and painful ecchymotic areas were noted at the site of injection. No necrosis or sloughing of skin was seen. At no time was

vals. Gold *et al.*<sup>4</sup> stated that many of these were able to control their edema if taught to administer the mercurial diuretic to themselves with their weight as a guide, a situation paralleling that in diabetes mellitus. The ease of subcutaneous injection of Thiomerin, therefore, may prove to be one of its most important advantages.

**Summary.** 1. A new mercurial diuretic (Thiomerin) for subcutaneous administration has been used with excellent results with 2069 injections in 409 patients.

2. Thiomerin has advantages over other mercurial diuretics: *a.* There is no apparent systemic toxicity. *b.* It is practically painless when given sub-

cutaneously. *c.* It is equally or more effective than other mercurial diuretics. *d.* Self-administration by a patient under a physician's direction is possible.

The authors wish to express their appreciation to Mrs. Sarah Prieb, R.N., Dr. William Strecker, Dr. Quentin Young, and the medical residents in the Cardiac Clinic for their help in preparing this report.

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# THE TOXICITY OF INTRAVENOUS AMMONIUM COMPOUNDS

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FOLLOWING Haldane's<sup>5</sup> demonstration in 1921 that the cation ( $\text{NH}_4^+$ ) of ammonium chloride is metabolized in the body to urea thus freeing an equivalent amount of anion ( $\text{Cl}^-$ ), this salt has been used both orally and intravenously as an acidifying agent in the treatment of clinical alkalosis. Its successful intravenous use in one patient was first reported by McCann<sup>8</sup> in 1922 and in another in 1925 by Youmans and Greene<sup>13</sup>. After Gamble and Ross<sup>3</sup> pointed out that this salt may cause sodium depletion and dehydration, enthusiasm for its intravenous use lessened. These workers advised that therapy consist simply of presenting the kidney with adequate amounts of fluid and sodium chloride on the physiologic presumption that the selective excretion of the cation ( $\text{Na}^+$ ) would compensate for the alkalosis. However, the rationale of this procedure may be questioned since it postulates a normally functioning kidney, while actually renal damage or functional insufficiency may occur in alkalosis (Nicol<sup>10</sup>, 1940). In 1943 Zintel, Rhoads and Ravdin<sup>15</sup> resumed the use of intravenous ammonium chloride and reported the successful treatment of 7 patients in alkalosis. Several subsequent reports indicate that the infusion of this salt may be a valuable therapeutic measure<sup>2,11,12</sup>.

In view of the increasing clinical use

of parenterally administered ammonium chloride, it would seem worth while to review our knowledge of its pharmacologic effects and toxicity.

PHARMACOLOGIC EFFECTS. As early as 1893 Marfori<sup>7</sup> described the principal effects produced by injected ammonium chloride in animals as twitches, tremors progressing to tetany, violent convulsions, opisthotonus, irregular respiration, salivation, emesis, somnolence and lassitude. Meneguzzi<sup>9</sup> reported in 1912 that if ammonium chloride injection was not immediately fatal, the body functions recover rapidly from the effects. Recently (1946), Brassfield *et al.*<sup>1</sup> showed that intravenous ammonium chloride produced an immediate increase in respiration, fall in blood pressure, and slowing of the heart. More pertinent was the report in the same year by Forbes and Erganian<sup>2</sup> who supplemented their clinical studies with some experimental results. They found that 20 to 30 cc. of 0.89% ammonium chloride per kilogram body weight could be injected into dogs and rabbits producing only symptoms of excessive salivation, hyperpnea and drowsiness, but that a *more rapid rate of injection* produced stupor and convulsions. Koenig and Koenig<sup>6</sup> reported in 1948 that intravenous ammonium chloride can produce pulmonary edema. Ammonium compounds are also reported to have a weak curarizing action on skeletal

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muscle, a stimulant effect on the central nervous system, and an expectorant effect.

**TOXICITY IN PATIENTS.** Forbes and Erganian<sup>2</sup> reported that one infant showed pallor, irregular respiration, occasional twitchings of the eyelids and hands, bradycardia and poor response to painful stimuli following the intravenous administration of 30 cc. per kg. of 0.89% ammonium chloride over the course of 18 minutes. They attributed these toxic signs to a too rapid injection with extensive fall in serum pH. Schemm<sup>12</sup> (1947), though using only a 0.46% solution of ammonium chloride, observed minor toxic signs in 5 patients consisting of pallor, sweating and retching. Strangely enough, in the 2 series of patients<sup>12,14</sup> given the higher concentration of 2% ammonium chloride, no toxic reactions were reported.

These diverse reports and the fact that toxic reactions may occur clinically from intravenously injected ammonium chloride indicate a need for further experimental study. We have undertaken the following laboratory investigation for the purpose of (a) elucidating the nature and mechanism of the toxic reactions produced by intravenous ammonium chloride and (b) furnishing a basis for deciding how ammonium chloride solutions should be given for maximum safety and effectiveness.

**EXPERIMENTAL. 1. Method.** Healthy, adult dogs of either sex were anesthetized after a 24 hour fast with 34 mg. per kg. of sodium pentobarbital intravenously. A dry, crystalline, reagent quality of ammonium chloride was dissolved in sterile 5% dextrose of solution to make the final solution 2% in ammonium chloride. In order to determine the toxicity of the ammonium radical independent of the acidifying effects of ammonium chloride, we also used solutions of 2.88% ammonium acetate, 2.96% ammonium bicarbonate, and 2.0 and 2.5% ammonium carbonate prepared in the same way. The solutions were infused into the femoral vein at arbitrary rates controlled and checked by frequently counting the drops per 30 second period in the intravenous ap-

paratus. At the end of each experiment the rate of infusion in cc. per minute was determined by counting the number of drops per cc. The rate of infusion was then calculated to milliequivalents (0.001 gm. equivalent weights) of ammonium ion per minute, and finally as milliequivalents of ammonium ion per minute per kg. of body weight. Carbon dioxide combining power of plasma was determined by the Van Slyke and Neill manometric method<sup>14</sup>.

**2. Results.** A typical sequence of toxic signs was observed in almost all experiments, regardless of the particular ammonium compound used. In 28 of the 32 animals studied, the onset of toxic signs was indicated by occasional deep inspiratory gasps followed by a marked expiratory effort with strong contraction of the abdominal muscles. These gasps became more frequent and pronounced until the respiration became very irregular, with each gasp accompanied by a marked ventral "jerking" of the head. Simultaneously the heart rate slowed down and the systolic blood pressure increased, although the diastolic pressure was unchanged so that an increased pulse pressure resulted. Next, muscular twitchings were noticed, usually beginning about the angles of the mouth, spreading to the other muscles of the face and neck, and accompanied by fasciculations of the tongue. These twitchings quickly spread throughout the body and tonic and clonic convulsions followed. Unless the infusion was promptly stopped, death ensued from respiratory arrest with the heart beat continuing for several seconds after respiration ceased. Also noticed were occasional cardiac irregularities, auscultatory sounds characteristic of fluid in the lungs, as reported by Koenig and Koenig<sup>6</sup>, and hemolysis of the red blood cells of varying degree in all blood specimens drawn.

In 20 experiments, the infusion was allowed to continue until the death of the animal. Death occurred from 11 to



70 minutes after the earliest definite evidence of toxicity, considered usually as the onset of twitchings of the facial muscles or fasciculations of the tongue. In 4 dogs, however, the typical warn-

ing signs of toxicity did not appear. In one instance the first evidence of toxicity was a tonic convulsion, followed immediately by death. Another animal showed some tendency to gasping res-

TABLE 1.—INTRAVENOUS INJECTION OF VARIOUS AMMONIUM SALTS IN 5% GLUCOSE SOLUTION GIVEN TO DOGS

| AMMONIUM<br>SALT<br>GIVEN                      | WEIGHT<br>OF DOG<br>(kg.) | RATE OF<br>ADMINISTRATION |                      | INJECTION<br>RATE<br>mEq./kg./min. | ONSET OF<br>TOXIC<br>SIGNS<br>(mins.) | IRE/IRc |
|--|---------------------------|---------------------------|----------------------|------------------------------------|---------------------------------------|---------|
|  |                           | ml./min.<br>(aver.)       | mEq./min.<br>(aver.) |                                    |                                       |         |
| 2% $\text{NH}_4\text{Cl}$                      | 14.1                      | 3.88                      | 1.45                 | 0.103                              | 63                                    | 2.29    |
|  | 10.9                      | 3.39                      | 1.27                 | 0.116                              | 63                                    | 2.58    |
|  | 21.4                      | 7.67                      | 2.86                 | 0.133                              | 45                                    | 2.69    |
|  | 10.9                      | 3.61                      | 1.35                 | 0.124                              | 34                                    | 2.76    |
|  | 6.4                       | 3.19                      | 1.19                 | 0.143                              | 64                                    | 3.18    |
|  | 7.3                       | 2.93                      | 1.10                 | 0.151                              | 32                                    | 3.36    |
|  | 17.7                      | 8.43                      | 3.15                 | 0.178                              | 17                                    | 3.96    |
|  | 7.7                       | 3.98                      | 1.49                 | 0.193                              | 42                                    | 4.29    |
|  | 8.2                       | 4.25                      | 1.59                 | 0.194                              | 36                                    | 4.30    |
|  | 10.9                      | 5.83                      | 2.17                 | 0.199                              | 31*                                   | 4.42    |
|  | 12.5                      | 7.33                      | 2.74                 | 0.219                              | 18                                    | 4.87    |
|  | 12.9                      | 7.69                      | 2.88                 | 0.223                              | 14                                    | 4.96    |
|  | 7.2                       | 4.67                      | 1.74                 | 0.242                              | 11                                    | 5.37    |
|  | 6.7                       | 5.26                      | 1.97                 | 0.292                              | 8                                     | 6.48    |
|  | 70.0                      | 8.34                      | 3.12                 | 0.045                              | 60                                    |         |
| $\text{NH}_4\text{Cl}$ used clinically in man. |                           |                           |                      |                                    |                                       |         |
| 2.88% Ammonium                                 | 10.5                      | 5.52                      | 2.06                 | 0.196                              | 50                                    | 4.35    |
| Acetate  | 11.4                      | 6.06                      | 2.27                 | 0.199                              | 39                                    | 4.42    |
| 2.0-2.5% Ammonium                              | 13.3**                    | 3.84                      | 1.68                 | 0.127                              | 57                                    | 2.82    |
| Carbonate                                      | 10.8***                   | 4.90                      | 1.71                 | 0.159                              | 38                                    | 3.54    |
| 2.96% Ammonium                                 | 10.8                      | 3.30                      | 1.23                 | 0.114                              | 27                                    | 2.53    |
| Bicarbonate                                    | 15.0                      | 5.30                      | 1.98                 | 0.132                              | 40                                    | 2.94    |
|  | 13.6                      | 4.87                      | 1.82                 | 0.133                              | 66                                    | 2.95    |
|  | 6.3                       | 2.28                      | 0.85                 | 0.137                              | 50                                    | 3.03    |
|  | 10.0                      | 3.66                      | 1.37                 | 0.137                              | 24                                    | 3.04    |
|  | 10.9                      | 4.05                      | 1.52                 | 0.138                              | 30                                    | 3.06    |
|  | 7.2                       | 2.79                      | 1.03                 | 0.143                              | 20*                                   | 3.17    |
|  | 13.3                      | 5.65                      | 2.12                 | 0.159                              | 25                                    | 3.54    |
|  | 13.6                      | 6.13                      | 2.29                 | 0.168                              | 30                                    | 3.73    |
|  | 13.3                      | 6.00                      | 2.24                 | 0.169                              | 50                                    | 3.77    |
|  | 5.9                       | 2.74                      | 1.03                 | 0.173                              | 28                                    | 3.82    |
|  | 6.8                       | 3.30                      | 1.23                 | 0.182                              | 15                                    | 4.05    |
|  | 10.9                      | 5.72                      | 2.14                 | 0.197                              | 18                                    | 4.37    |
|  | 8.9                       | 5.21                      | 1.95                 | 0.219                              | 27                                    | 4.87    |

\* Dog died at that time

\*\* 2.5%

\*\*\* 2.0%

The columns reading from left to right show in order the weight of the dog in kg., the average rate of infusion of the ammonium salt in ml. per min., the average rate of infusion in mEq. per min., the average rate of infusion of the ammonium compound in mEq. per kg. per min., and the length of time from start of infusion to onset of unmistakable toxic signs. The data listed under the quotient IRe/IRc in the last column is the Injection Rate in that particular experiment expressed in mEq. per kg. body weight per min. (IRe for Injection Rate, experimental) over the Injection Rate used clinically by Zintel, Rhoads and Ravdin<sup>15</sup> and Sellers and Kast<sup>12</sup> recalculated to the same units (IRc for Injection Rate, Clinical) which amounts to 0.045 mEq. per kg. per min.

piration with a little trembling at the end of inspiration, and then quietly ceased breathing. The third animal showed some respiratory irregularity and then died of respiratory arrest without muscular twitchings or other warning signs. The fourth atypical dog showed several gasping respirations immediately followed by 2 successive tonic convulsions, vomited, and died of respiratory failure, possibly from aspirated vomitus.

The data for the onset of toxicity in all 32 dogs are summarized in Table 1. These data show that definite toxicity

of death. Ammonium chloride consistently caused a fall in carbon dioxide combining power; ammonium bicarbonate usually caused a slight rise, and ammonium acetate no consistent change in the 2 cases studied. The sequence of toxic events, however, was the same regardless of the direction or amount of change in carbon dioxide combining power.

**Discussion.** The results shown in Table 1 indicate that the appearance of toxic signs from ammonium chloride administration are related to the rate of administration rather than the total

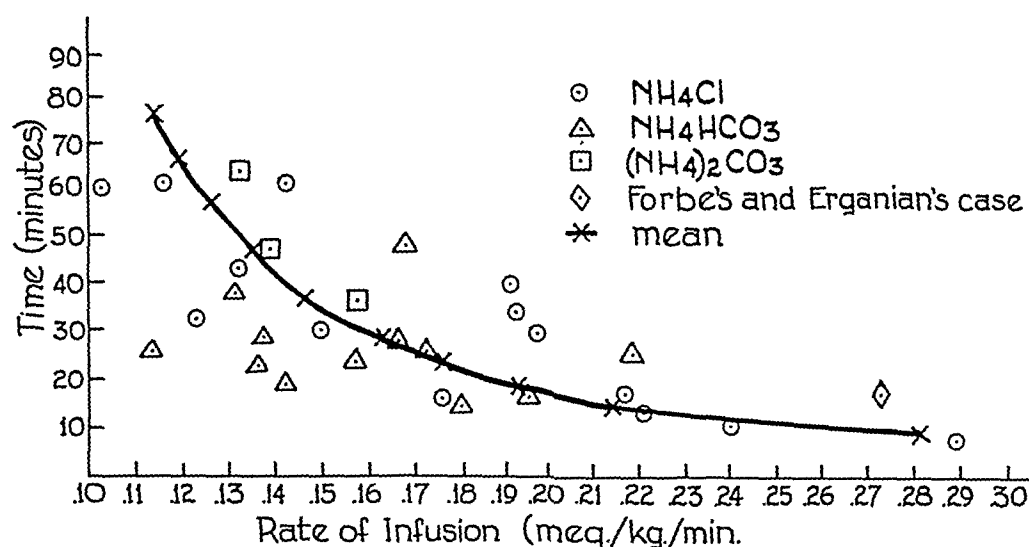


FIG. 1.—Relationship between rate of infusion and time to onset of toxicity.

was observed with rates of infusion as low as 2.3 times that which had been used clinically, while a rate of 6.45 times produced toxic signs in 8 minutes.

Fig. 1 shows the time of onset of toxicity in minutes plotted against the average rate of infusion in milliequivalents of ammonia per minute. It will be observed that the curve is roughly hyperbolic, and that no consistent difference is observed between the several ammonium compounds used.

Table 2 lists the carbon dioxide combining power of the blood, when ammonium salts were injected, before injection, at the onset of definite toxic signs, and at or within 1 to 2 minutes

TABLE 2.—EFFECT OF INJECTION OF AMMONIUM SALTS ON CARBON DIOXIDE COMBINING POWER OF BLOOD

| Ammonium Compound Used | Before Injection Vols. % | Onset Toxicity Vols. % | At Death Vols. % |
|------------------------|--------------------------|------------------------|------------------|
| Ammonium Chloride      | 56                       | •                      | 4.0.             |
|                        | 52.5                     | 48.5                   | 11               |
|                        | 40.5                     | 24.5                   | 18               |
|                        | 46.5                     | 31                     | 27               |
|                        | 44.8                     | 36                     | 21.6             |
| Ammonium Carbonate     | 50                       | •                      | 63               |
|                        | 53                       | 61                     | 53.5             |
|                        | •                        | 44                     | 56               |
|                        | 39                       | 53                     | 46               |
|                        | •                        | •                      | 50.1             |
| Ammonium Acetate       | 53                       | 45                     | 46.5             |
|                        | 43                       | 47                     | 49               |

• No determination made because of technical error.

amount injected. The influence of the rate of injection on toxicity was suggested in the earlier experiments of Meneguzzi<sup>9</sup> who found that animals recovered rapidly from the effects of ammonium chloride if the injection was not immediately fatal and Forbes and Erganian<sup>2</sup> who reported that more rapid rates of injection were more likely to produce severe toxic symptoms. Also, this is probably the reason for the appearance of toxic symptoms reported by Forbes and Erganian in the infant who received 30 cc. per kg. intravenously of 0.89% ammonium chloride within 18 minutes. We have recomputed the data given for the rate and amount of salt injected into this infant and find that it amounts to 0.276 milliequivalents per kg. per minute. This is entirely consistent with the rate and time of administration which produced toxic signs in our experiments on dogs (column 5, Table 1 and Fig. 1). This comparison would suggest that our data on dogs may with reasonable safety be applied to human beings. If so, the IRe/IRc ratio listed in Table 1 is seen to be uncomfortably low in some cases. Thus, rates of administration as low as 2.29 times that used clinically could produce toxic signs in patients. This is significant in view of the ease with which an intravenous infusion may, if not constantly attended, flow into the vein in half or less the intended time. It would therefore seem wise to reduce the concentration and, or, the volume per hour, in order to decrease the risk of producing toxic reactions in patients. The occasional death of an animal in our studies with no warning signs re-emphasizes the importance of maintaining a wide safety margin.

Probably because the therapeutic value of ammonium chloride depends largely on its acidifying action, attention has been focused upon this action as the cause of toxicity. Forbes and

Erganian attributed the toxic signs in their patient to a too rapid injection with extensive fall in serum pH. Since, however, we have been able to produce identical toxic signs with ammonium compounds which are acidifying, alkalizing, or neutral in their physiologic reactions, it is more likely that the toxicity is due to the ammonium ion *per se*, and not to changes in serum pH. In the experiments where we determined carbon dioxide combining power (Table 2), toxic signs and even death occurred without significant changes from the normal carbon dioxide combining power.

Another possibility which should be considered is that the toxicity of ammonium compounds might depend upon the relative fractions existing as  $\text{NH}_4^+$  and as  $\text{NH}_3$  or  $\text{NH}_4\text{OH}$ . In aqueous solution there is considerable variation in the amount of hydrolysis from moderate in ammonium chloride to considerable in ammonium acetate and bicarbonate. However, at the approximate pH of blood the amount of  $\text{NH}_3 + \text{NH}_4\text{OH}$  would always be small relative to  $\text{NH}_4^+$  regardless of the variation of pH within the physiological limits.

It might be argued that the anesthetic used (sodium pentobarbital) would interfere with the translation of our results to unanesthetized patients. However, the close quantitative comparison between our results and the single toxic reaction observed by Forbes and Erganian would indicate that there has been little interference by the anesthesia. Furthermore, we have consistently noticed a tendency for the anesthesia to become lighter after administration of ammonium ions was commenced, as evidenced by return of deep tendon reflexes and of the wink reflex. This would suggest, as has been previously reported, that ammonium ions have a central stimulant effect, and that if anesthesia exerted any

influence on the toxicity of ammonium compounds, it would be in the direction of protection rather than enhancement.

The hyperbolic form of the mean curve in Fig. 1 suggests that there is a slow rate of infusion of ammonium compounds which can be tolerated for long periods of time, probably because it is below the rate at which the liver can successfully convert all of the ammonium ion to urea. Conversely there is apparently a minimum time of several minutes which must elapse before toxic signs develop, no matter how high the rate. There is, however, a clear correlation between rate of administration of ammonium ion and the appearance of toxicity. No apparent correlation exists between total amount given and toxicity.

We believe, therefore, that the safety of any clinical procedure using ammonium chloride intravenously depends upon the rate at which it is administered rather than the total amount used. This is a significant fact in clinical practice, as the value of ammonium chloride either as an acidifying agent or as diuretic depends upon the conversion of the ammonium ion to urea, freeing the chloride ion. Consequently, exceed-

ing the maximum rate at which this conversion can be accomplished does not increase either the rapidity or effectiveness of therapeutic action. The therapeutic effects of ammonium chloride are a function of the total amount administered and not of the rate. Conversely, the toxicity is a function of the rate and not of the total amount. Hence, clinical safety without impaired efficiency may be gained by the slow administration of proper amounts of ammonium chloride.

**Summary and Conclusion.** 1. Intravenously injected ammonium chloride, though a valuable therapeutic agent, has definite toxic potentialities.

2. Occurrence of toxicity is dependent upon rate of intravenous administration, and virtually independent of total amount administered. Therapeutic value, on the other hand, depends upon amount administered regardless of rate. Therefore, slow rates of administration are safer without loss of effectiveness.

3. Toxic reactions to ammonium chloride are due to the ammonium ion and not to the acidifying effect of the compound, since the same effects may be produced by the carbonate or acetate salt without accompanying acidosis.

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# ALTERATIONS IN THE SERUM POTASSIUM AND THEIR RELATION TO CERTAIN CONSTITUENTS OF THE BLOOD IN DIABETIC ACIDOSIS\*

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RECENT studies have shown that serum potassium concentrations may be lowered critically during therapy for diabetic acidosis<sup>19,23,31</sup>. The severity with which the skeletal muscle and cardiovascular systems are sometimes affected, as well as the dramatic reversal of the symptoms during the administration of potassium, suggests an electrolyte imbalance of a selective type. The striking manifestation of potassium deficiency that has been encountered in association with low potassium in the serum was first recognized and studied in patients with familial periodic paralysis<sup>1,2,6,20,33,36,40</sup>. Later studies revealed that patients with other conditions such as diarrhea<sup>12,13,22</sup>, prolonged vomiting<sup>5</sup>, and Cushing's Disease<sup>35</sup> often exhibited manifestations of potassium deficiency.

As our investigations progressed, the importance of potassium depletion in patients with diabetic acidosis became increasingly apparent. This report describes the changes in the serum potassium and their relation to certain other constituents of the blood in 45 patients with diabetic acidosis.

**Methods and Materials.** The diagnosis of diabetic acidosis was established by the usual clinical criteria; these included a carbon dioxide combining power of less than 14 mEq. per liter and a blood sugar greater than 200 mg. per 100 ml.

Upon admission to the hospital, venous blood was taken for determination of the blood sugar<sup>32</sup>, plasma carbon dioxide combining power<sup>41</sup>, pH (using a Cambridge pH meter and precautions to avoid loss of carbon dioxide), protein<sup>28</sup>, chloride<sup>34</sup>, blood urea nitrogen<sup>24</sup>, calcium<sup>10</sup>, sodium† and potassium<sup>2</sup>. These studies were repeated at intervals varying from 1 to 12 hours after

\* This study includes a portion of the data obtained in the course of an investigation of diabetic acidosis at the Philadelphia General Hospital. This work was aided by a research grant from the United States Public Health Service.

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† The sodium and potassium determinations were made on a Perkin-Elmer flame photometer, Model 18, after precipitation of the serum proteins with trichloroacetic acid. Normal values by this method are: Na, 136 to 152 mEq./l; K, 4.1 to 5.1 mEq./l. The instrument was standardized frequently during runs by means of a series of solutions of known sodium and potassium concentration. Recoveries of potassium added to serum ranged from 100 to 110%, averaging 105%, while sodium recoveries varied between 94 to 100% with an average of 97%. When determinations were made in duplicate, the precision of the potassium determinations

calculated as  $\sigma = \sqrt{\frac{\sum (X_1 - X_2)^2}{n}}$  was 0.55 mEq. where  $n$  is the total number of determinations

(2 times the number of pairs) and  $x_1 - x_2$  represents the difference between duplicates.

the first administration of insulin until the clinical condition, the chemical, and the electrocardiographic findings showed marked improvement. The complete quantitative collection of urine samples during the first 12 hours was often attempted but was satisfactory in only 1 patient. Anuria or loss of sphincter control interfered in the others. Catheterization in these patients involved hazards that we believed unwarranted to assume.

All patients received regular insulin subcutaneously in divided doses, the total amount varying from 50 to 1,300 units. Each was given at least 2,000 ml. of isotonic sodium chloride solution by hypodermoclysis but none received more than 3,000 ml. in the first 12 hours. The total amount of fluid administered during the second 12 hours

varied between 1,000 and 3,000 ml. Nearly all patients received 16 gm. of sodium bicarbonate in 2 gm. portions every 20 minutes by the oral route; others received 11.25 gm. of sodium bicarbonate dissolved in 500 ml. of distilled water by intravenous injection. When the blood sugar had decreased to approximately 250 mg. per 100 ml., glucose was administered in 25 gm. portions by means of a Levine tube; the total dose depended upon the blood sugar level. Shock, if encountered, was treated by the administration of plasma, and occasionally, whole blood.

Potassium chloride was administered parenterally when the serum potassium was low, either as an isotonic solution of potassium chloride (155 mEq. per liter) or an isotonic mixture of equal parts of sodium chloride

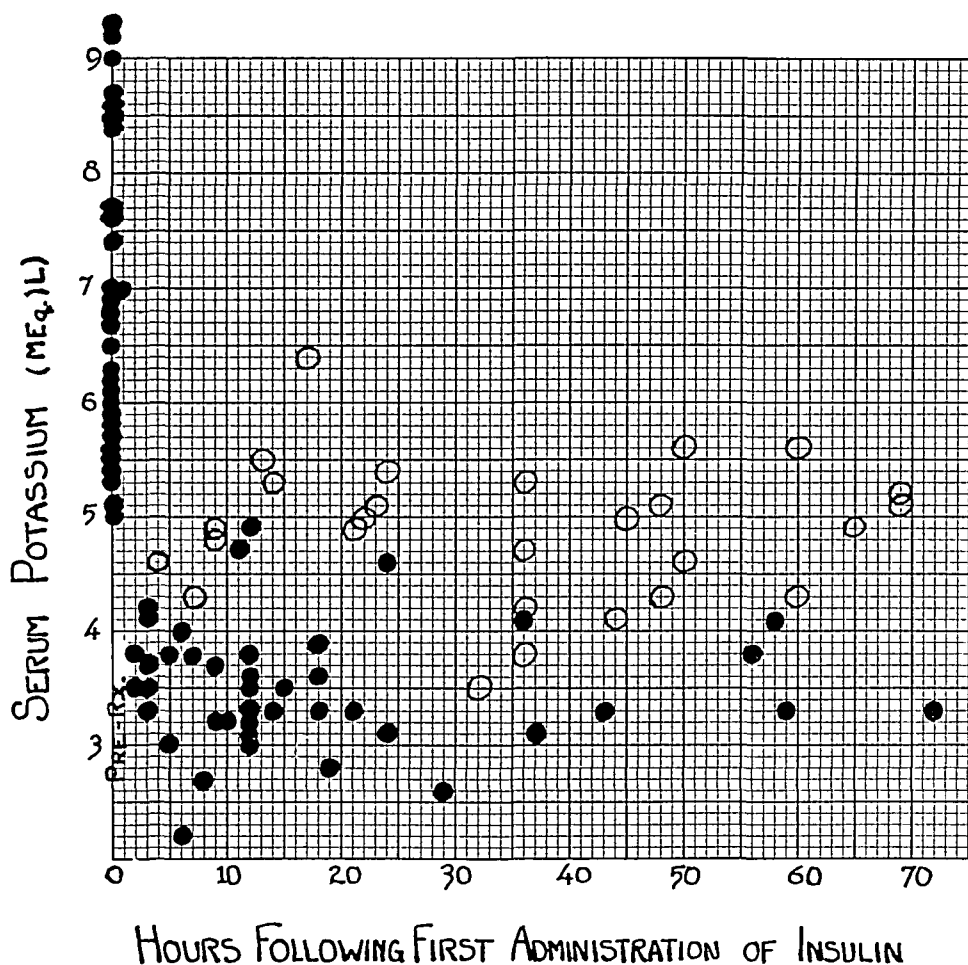


FIG. 1. Serum potassium concentrations before and after insulin in 45 patients with diabetic acidosis. Before insulin treatment the serum potassium level was normal or elevated. In the period of 2 to 18 hours following the first administration of insulin the serum potassium concentration decreased to levels below normal and remained subnormal until potassium or food containing potassium was administered. Open circles refer to values obtained after potassium or a food containing potassium was administered.

This information has been presented in part by Martin and Wertman<sup>29</sup>.

and potassium chloride. Twelve patients received the former. This concentration is more concentrated than that suggested by Darrow<sup>13</sup> and Burnett and Burrows<sup>8</sup>. However, our experience indicates that it was more effective in replenishing the potassium deficit, yet not dangerous to administer if controlled by serial electrocardiograms. When potassium was given by hypodermoclysis to prevent a decrease in the serum potassium, a mixture of equal parts of potassium chloride and sodium chloride was used.

### Results. Concentration of the Serum Potassium Before and After Therapy.—

Fig. 1 shows the serum potassium concentrations before and after the institution of insulin therapy together with the response of serum potassium to potassium administration. It will be noted that before insulin treatment the concentration of potassium in serum varied from 5 mEq./l to 9.3 mEq./l. In no instance was the serum potassium

concentration below normal during this period of observation. The results in Table 2 indicate that the state of circulatory collapse in anoxia is not the main factor in the higher serum potassium values.

Soon after insulin treatment was instituted, however, the serum potassium decreased to concentrations below the minimal normal. This fall occurred within 2 hours after the first administration of insulin in some patients. More commonly, however, the lowest level was reached later, between the 3rd and 18th hour. Some low values persisted into the 3rd day. The return to normal concentrations did not occur until potassium was administered or a food containing potassium was eaten. Fig. 1 shows also the rise in serum potassium accomplished by potassium infusion.

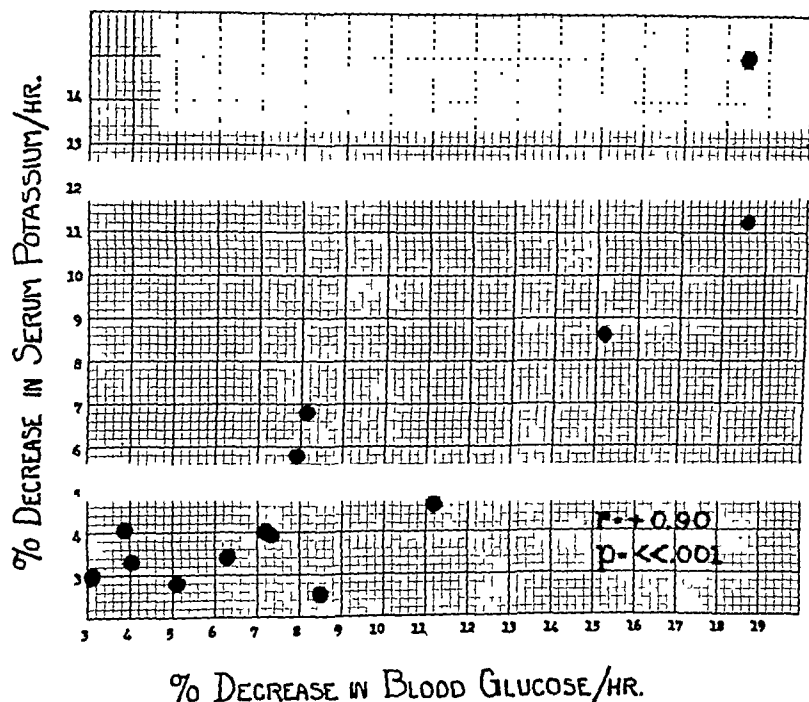


FIG. 2. The decrease in blood glucose following insulin compared to the decrease in serum potassium, both expressed as per cent decrease per hour. The rate of fall of the blood sugar appears to offer a rough index of the rapidity with which the serum potassium decreases in these patients receiving active therapy for diabetic acidosis.

*Correlation of the Insulin Effect and the Serum Potassium Concentration.*—Fig. 2 shows the relationship between the action of insulin and the serum potassium in patients undergoing treatment for diabetic acidosis. The decrease in the blood glucose per hour was taken as a measure of the insulin effect. A high degree of correlation was found between the decrease in the serum potassium and the decrease in the blood glucose, both expressed as per cent decrease per hour. Calculation

factors, such as a greatly increased loss of potassium in the urine or continuous potassium administration, might modify the rapidity with which the serum potassium decreases without comparable effects on the blood sugar.

*Serum Potassium and the Blood pH.*—Fig. 3 shows the relationship of serum potassium and the blood pH in diabetic acidosis. Low pH is associated with high concentration of serum potassium; as the pH rises, the concentration of potassium falls to values

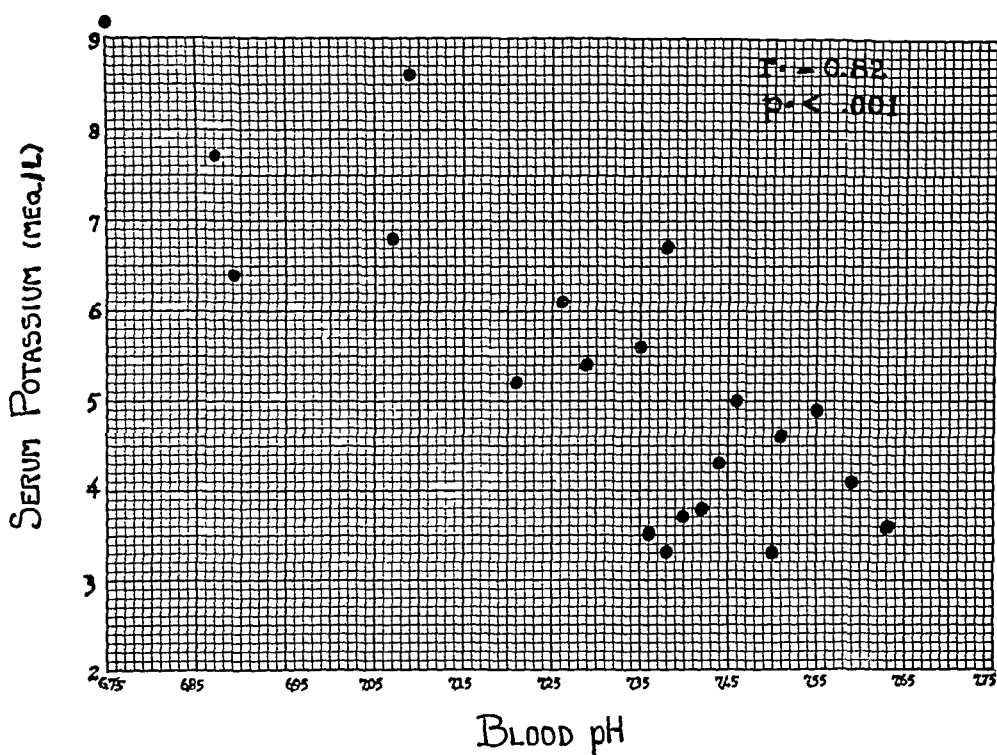


FIG. 3. The relationship of the serum potassium concentration to the blood pH before and during therapy for diabetic acidosis.

of the coefficient of correlation shows a value of 0.90, which is highly significant. Thus, the rate of fall of the blood sugar in these patients provides a crude index of the rapidity with which the serum potassium decreases. Obviously no more than a general conclusion can be derived concerning potassium from this chart. Furthermore, in patients undergoing treatment for diabetic acidosis, other

below normal. The coefficient of correlation is 0.82, which is highly significant.

A negative correlation exists between the serum potassium level and the carbon dioxide combining power. The coefficient of correlation was minus 0.54 (Fig. 4), a statistically significant value.

No correlation was found between the serum potassium and the serum cal-



cium, carbon dioxide tension, serum total base, chloride, protein, blood urea nitrogen, or hemoglobin.

*Distribution of Potassium.* More detailed information concerning the influence of various factors affecting potassium exchange in diabetic acidosis is shown in Table 1, which summarizes the response of a patient during the 24 hours following administration of insulin. This patient's symptoms were moderate by comparison with those of the others studied and to this extent he

during this 3 hour period and it contained only 3.0 mEq. of potassium. Although the patient received no fluid during this period, the decrease in hemoglobin concentration suggests that his blood volume and extracellular volume had expanded by approximately 1.5 liters due to transfer of water from the cellular phase. Approximately 5 mEq. of potassium is accounted for by this decrease in concentration of potassium in the extracellular fluid. Estimating the extra-

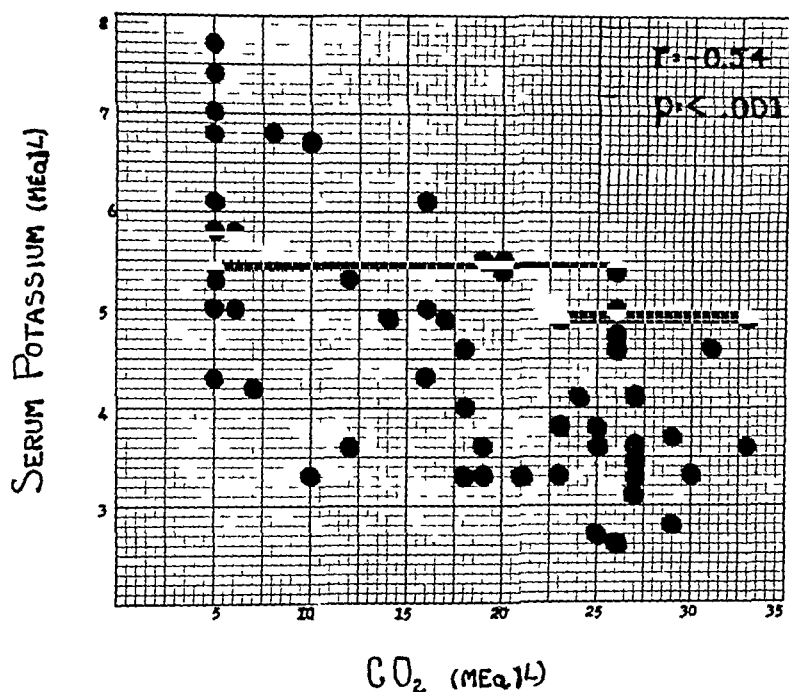


FIG 4 Serum potassium concentration and carbon dioxide combining power of serum before and during therapy for diabetic acidosis

is not typical of the group. He did, however, show a characteristic decrease in serum potassium concentration following insulin from a high normal of 5.4 mEq./l to 3.4 mEq./l, three hours later. At the same time the blood pH rose 0.07 while the serum sodium rose 10 mEq./l and the total base showed a comparable increase. The output of urine was only 200 ml.

cellular fluid volume of the 55 kg. man at 8,500 to 10,500 depending on the degree of dehydration, the total amount of potassium in the extracellular fluid at 5.4 mEq./l concentration would be 46 to 57 mEq. and at 3.5 mEq./l, 29 to 36 mEq. Thus 17 to 21 mEq. of potassium disappeared from the extracellular fluid and of this only 8 mEq. can be accounted for in the urine and

expanded extracellular fluid volume. The remainder constituting the larger portion of the potassium that disappeared thus must have entered the cells. However, if sodium chloride had been administered, a much larger increase in the urinary excretion of potassium might have been expected and perhaps a more striking decrease in serum potassium would have occurred.

The transfer of sodium from the cells to the extracellular phase that appears to have occurred in this patient following insulin administration is noteworthy, ranging from 295 to 335 mEq. Darrow has demonstrated a similar reciprocal relationship between sodium and potassium in several diseased states<sup>13</sup>.

**Discussion.** The changes in the potassium economy that occur in diabetic acidosis can be separated into 2 phases. The prodromal stages are characterized by loss of potassium from the body while potassium intake is at the same time likely to be negligible. Available evidence indicates that total body potassium is depleted. However, the potassium concentration in the serum is normal or elevated. The second phase occurs after therapy has been instituted. The total body potassium remains decreased, and the concentration in the serum falls below normal.

Atchley, *et al.*<sup>3</sup> found that potassium comprised a large proportion of the base lost in the urine during the development of diabetic acidosis. Equally important was their finding that a substantial loss of potassium in the urine occurred during the glucosuria and diuresis which preceded the actual acidosis. With the decline in the blood pH and the accompanying increase in urinary nitrogen excretion, the patients show an augmented loss of potassium in the urine. These findings have been confirmed by Butler, *et al.*<sup>9</sup>

Wiley, Wiley, and Waller<sup>42</sup>, and Elkinton and Winkler<sup>15</sup> also have demonstrated that increased urinary excretion of potassium occurs during dehydration, acidosis, and diuresis. Tarail and Elkinton<sup>39</sup> have studied patients during periods of low potassium intake; their results indicate that under these conditions more potassium is lost in the urine than in the gastrointestinal fluid and furthermore, that potassium is not completely reabsorbed by the renal tubules during this period of maximum need for the ion.

Vomiting commonly accompanies the onset of diabetic acidosis and increases the amount of potassium lost from the body. Austin and Gammon<sup>4</sup>, and Frenkel, Groen, and Willebrands<sup>19</sup> have reported that gastric juice and vomitus contain a higher concentration of potassium than does blood serum; they found concentrations as high as 10 to 13 mEq. per liter in gastric juice as well as vomitus.

Anorexia also is a characteristic finding in patients developing diabetic acidosis. A decreased intake of food would contribute to a negative balance of potassium.

**Serum Potassium Before Therapy.** Martin and Wertman<sup>29</sup> showed that the serum potassium level may be elevated before therapy in the diabetic patient in acidosis. The cause of a normal or elevated serum potassium concentration, which occurs at a time when the total body concentration of this cation is depleted, needs further study. Oliguric and anuric states are associated with a high serum potassium in some patients with uremia<sup>25,26,37,38</sup>. Thus, in renal insufficiency, a common complication of diabetic acidosis, high serum potassium levels were present when the renal output of potassium was increased.

Infants with diarrhea and severe dehydration show a normal or elevated serum potassium before therapy; Dar-

row states that the elevated serum potassium in these patients bears some relation to the state of anoxia and morbidity<sup>12</sup>. A similar cause may be present in some patients with diabetic

acidosis. However, the patients with diabetic acidosis in our series showed no relationship between the higher levels of serum potassium before therapy and the state of circulatory

TABLE 1. THERAPY AND METABOLIC DATA OF A 55 KG. COLORED MALE WITH DIABETIC ACIDOSIS

| HOURS     | SERUM CONCENTRATIONS |                |                            |               |                       |                      |              |                   |                  |                 |                    |
|-----------|----------------------|----------------|----------------------------|---------------|-----------------------|----------------------|--------------|-------------------|------------------|-----------------|--------------------|
|           | Sugar<br>(mg/100 ml) | pH             | CO <sub>2</sub><br>(mEq)/l | Cl<br>(mEq)/l | Total Base<br>(mEq)/l | Na<br>(mEq)/l        | K<br>(mEq)/l | Ca<br>(mg/100 ml) | Prol<br>(gm)     | Hb<br>(gm)      | BUN<br>(mg/100 ml) |
| Pre Ther. | 356                  | 7.29           | 11                         | 95            | 139                   | 130                  | 5.4          | 8.5               |                  | 14.4            | 10                 |
| 3         | 156                  | 7.36           | 17                         |               | 153                   | 140                  | 3.4          | 9.3               |                  | 12.4            |                    |
| 7         | 188                  |                | 23                         | 93            | 147                   | 135                  | 4.4          |                   | 6.9              | 11.7            | 17                 |
| 9         | 278                  |                | 23.4                       | 105           | 155                   |                      | 5.1          |                   | 6.5              | 12.1            | 18                 |
| 22        | 390                  |                | 17.6                       | 88            | 155                   |                      | 4.9          | 9.6               |                  | 12.0            | 12                 |
| HOURS     | THERAPY              |                |                            |               |                       | URINE CONCENTRATIONS |              |                   |                  |                 |                    |
|           | Insulin<br>units     | Fluids<br>(cc) | Na<br>(gm)                 | K<br>(gm)     | Prol<br>(gm)          | Total K<br>(mEq)     | K<br>(mEq)/l | Volume<br>(cc)    | N<br>(mg/100 ml) | Total N<br>(mg) |                    |
| 1         | 50                   |                |                            |               |                       | 1.0                  | 20.0         | 50                | 6.01             | 3.30            |                    |
| 2         |                      |                |                            |               |                       | 2.0                  | 13.1         | 150               | 4.13             | 6.19            |                    |
| 4         |                      | 750            | 6                          | 1.2           | 43                    | 16.7                 | 64.4         | 250               | 11.57            | 28.9            |                    |
| 5         |                      | 120            |                            |               |                       | 14.0                 | 46.6         | 300               | 11.10            | 33.31           |                    |
| 7         |                      | 120            |                            |               |                       |                      |              |                   |                  |                 |                    |
| 8         |                      |                |                            |               |                       |                      |              |                   |                  |                 |                    |
| 9         |                      | 120            |                            |               |                       | 8.5                  | 27.2         | 311               | 7.49             | 22.48           |                    |
| 11        |                      |                |                            |               |                       | 3.8                  | 19.2         | 200               | 6.45             | 12.90           |                    |
| 14        |                      |                |                            |               |                       | 6.5                  | 32.3         | 200               | 8.67             | 17.34           |                    |
| 19        |                      |                |                            |               |                       | 6.1                  | 30.5         | 200               | 9.38             | 18.76           |                    |

collapse (Table 2). The relationship which has been found to exist between potassium and glucose in metabolism as pointed out by Fenn<sup>17,18</sup> is more convincing. Glycogenolysis, with release of glucose and potassium in the blood stream without subsequent glycolysis, must be considered as an important source of the high serum potassium values before therapy.

*Serum Potassium Following Therapy.* Cardiovascular manifestations and skeletal muscle paralysis associated with hypokalemia occur in a certain group of patients receiving therapy for diabetic acidosis<sup>19,23,31</sup>. Martin and Wertman<sup>29</sup> reported that the serum potassium fell below normal 12 to 24 hours after insulin therapy was begun in 6 of 14 patients being treated for diabetic acidosis. Our findings, however, show that an abnormally low potassium concentration in the plasma occurred much more frequently. The serum potassium level decreased to less than the lower limit of normal, as early as 2 hours after insulin therapy was begun. Return to normal levels failed to occur until potassium chloride or potassium citrate was administered, or until food containing potassium was eaten.

*Importance of Potassium in Carbohydrate Metabolism.* After large doses of insulin a decrease in the serum potassium concentration occurs in experimental animals, normal patients, and in diabetics<sup>7,27</sup>. Low serum potassium concentrations have been demonstrated during the course of hypoglycemic shock in diabetic and psychotic patients<sup>13,14,21</sup>. We were able to find a significant correlation between the insulin effect (percentage of decrease in the blood glucose per hour) and the percentage of decrease in the serum potassium per hour in patients with diabetic acidosis. The fate of the potassium which leaves the serum is of importance, since, as

previously discussed, a deficiency of total body potassium exists at this time. Elkinton, Winkler and Danowski<sup>16</sup> present evidence that potassium does not enter the cells from the extracellular position unless an exogenous supply of this cation is present. Atchley, *et al.*<sup>3</sup> have shown that the urinary volume, as well as the urinary excretion of potassium, is very low after insulin therapy is begun in diabetic acidosis. Fenn's studies<sup>18</sup> in the rat indicate that potassium is preferentially deposited in the liver during glycogen formation. Thus, if part of the endogenous potassium which disappeared from the serum during the insulin treatment of patients with diabetic acidosis was not lost in the urine, it may be assumed that it must have entered the cells as is illustrated in Table 1. Since the evidence indicates that part of the potassium that disappeared from the serum entered the cells at the same time glucose did, one logical supposition is that the need for potassium brought about by restored metabolism of carbohydrate is responsible for the low values observed. Boyer, Lardy, and Phillips<sup>6a</sup> (1942) showed that potassium is essential to the resynthesis of adenosinetriphosphate. Further evidence that metabolism of glucose creates a demand for potassium is provided by Aitken, *et al.*<sup>1</sup> who reported that the serum level of this cation fell when 250 cc. of glucose were administered intravenously to normal subjects. Under conditions of greater stress and more marked depletion, a more marked response could be anticipated. Many investigators have observed the rapid decrease in the serum potassium level during the administration of glucose to patients with familial periodic paralysis<sup>20,36</sup>. It must be emphasized at this point, however, that the extremely low levels of serum potassium found during treatment of diabetic acidosis patients do not occur in controlled diabetic and

normal patients given equally large dosages of insulin with or without glucose.

An expanding extracellular space during administration of fluids has been postulated as the cause for the lowering of the concentration of serum potassium in patients with diabetic acidosis<sup>29</sup>. Undoubtedly, the omission of potassium from the fluids administered during the therapy plays some part in decreasing the serum potassium concentration. In patients receiving large amounts of fluids, followed by diuresis as occurred in the report by Holler<sup>23</sup>, this factor undoubtedly played

varies in different patients. All combine, however, to bring about acute depletion of intracellular and extracellular potassium that must be combated vigorously in the course of treatment.

This deficiency may be aggravated in these patients by the acceleration of the fall in serum potassium associated with rising pH of the blood. Thus, the important matter of the advisability of administering sodium bicarbonate or lactate during the treatment of diabetic acidosis comes into question. The answer must await further investigation.

TABLE 2. RELATIONSHIP OF THE SERUM POTASSIUM AND BLOOD PRESSURE TAKEN ON PATIENTS WITH DIABETIC ACIDOSIS BEFORE ANY THERAPY WAS BEGUN

| Highest Potassium Group     |  | High Normal Potassium Group |  |
|-----------------------------|--|-----------------------------|--|
| Serum Potassium<br>(mEq./l) | Blood Pressure<br>(Systolic/diastolic) | Serum Potassium<br>(mEq./l) | Blood Pressure<br>(Systolic/diastolic) |
| 9.3                         | 165/90                                 | 5.6                         | 40/20                                  |
| 9.3                         | 150/60                                 | 5.6                         | 140/80                                 |
| 9.2                         | 65/0                                   | 5.6                         | 40/20                                  |
| 8.9                         | 100/70                                 | 5.5                         | 85/60                                  |
| 8.6                         | 145/85                                 | 5.5                         | 110/70                                 |
| 8.6                         | 145/70                                 | 5.4                         | 110/60                                 |
| 8.6                         | 95/60                                  | 5.2                         | 90/60                                  |
| 8.5                         | 100/50                                 | 5.0                         | 165/90                                 |

The values were selected from the group with the highest potassium values (8.5 mEq./l to 9.3 mEq./l) and compared to those with high normals (5.0 mEq./l to 5.6 mEq./l). The blood pressures varied from shock levels to hypertensive in both groups.

an important role in the production of hypokalemia. However, the rapidity with which the potassium concentration decreased below normal, as well as our observation that the serum concentration fell in one patient to extremely low levels when no fluid was administered (Table 1), and in others after only 500 cc. of fluid had been given, indicates that this is not as important as the other factors mentioned.

The relative importance of the several factors operating to lower potassium concentrations in diabetic acidosis, namely: loss in urine or vomitus, starvation, dilution and transfer to the cellular phase, probably

**Summary.** 1. Alterations in the serum concentration of certain electrolytes were studied in 45 patients before and after therapy for diabetic acidosis.

2. The concentration of the serum potassium was consistently found to be normal or elevated before treatment and decreased below normal during the 2 to 18 hour period after insulin therapy was instituted. These sub-normal concentrations persisted until potassium or a food containing potassium was administered.

3. A relationship was found to exist between the rate of decrease in the blood glucose concentration and the serum potassium level.

4. Alteration of the blood pH was closely associated with the change in the serum potassium concentration, the serum potassium varying inversely with the blood pH. The serum potassium level was found to vary inversely with the carbon dioxide combining power.

5. The relationships of these findings to the need for administration of potassium during the treatment of dia-

betic patients in acidosis has been discussed.

We wish to thank Drs. E. S. Dillon and Anthony Sindoni, Physicians-in-Charge of the Metabolic Departments of the Philadelphia General Hospital for their cooperation in this study. Dr. S. S. Kety's advice concerning many aspects of the study was invaluable. We also wish to express our appreciation to the staff of the Diabetic Coma Project and to the nurses of the Metabolic Department for their assistance in this work.

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# THE INCREASED HYPOPROTHROMBINEMIC EFFECT OF A SMALL DOSE OF DICUMAROL IN CONGESTIVE HEART FAILURE

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BECAUSE of its action as an anti-coagulant, Dicumarol has assumed an important place in the treatment of thromboembolic disorders. One of its greatest fields of usefulness has been in cardiac diseases in the prevention of intracardiac thrombosis or embolism arising therefrom and peripheral deep vein thrombosis. The clinical condition of such patients may vary from very mild illness to a desperate state in which a considerable degree of congestive heart failure may occur. In a small number of such cases with right heart failure and systemic and hepatic congestion, we have observed an over-reaction to the usual doses of Dicumarol, so that excessive and sometimes dangerous degrees of hypoprothrombinemia have been induced. The following study was therefore undertaken to ascertain the pattern of reaction to Dicumarol in such patients as compared with a simultaneously observed series of normal individuals.

**Materials and Methods.** Thirty-six series of determinations (see below) were carried out in 23 patients. Eighteen of these were in moderate to severe right-sided cardiac failure and 5 were in mild failure. Thirteen of the former were available for restudy after improvement in the decompensation. An interval of 1 to 2 weeks elapsed before the testing was repeated. All patients were hospitalized and selected solely on the basis of having acute right-sided cardiac failure. Two were in the 3rd decade; the others were in the 5th, 6th and 7th decades. There were 16 males.

None had any clear-cut thromboembolic condition. The only consideration for rejection of a case in this series was the concomitant presence of organic renal or hepatic disease. Due to the congestion of the kidneys incident to heart failure and its attendant pre-renal deviation of fluid, impairment of kidney function may have been present in some of the cases, though in none was there any appreciable elevation of the blood urea. Depending upon the severity of cardiac failure, they were classified as absent or mild and moderate or severe. Patients with moderate or severe failure were those with markedly enlarged livers and with venous pressures over 15 cm. of blood, in whom rises in pressure usually occurred following manual compression over the liver. Moderate to marked peripheral edema was generally present. The only patients studied who were free of failure (normal venous pressure and absence of significant hepatomegaly) were those who had been tested previously while more severely decompensated and who had improved on therapy. All patients had minimal to moderate chronic left-sided failure. In most, some degree of right-sided failure had been present for months, but during this period they were ambulatory. All of the patients, however, had recently been precipitated over a period of days or weeks into more severe right heart failure. A considerable number had recovered from previous episodes of cardiac decompensation. The majority responded rapidly to conventional cardiac therapy; in these, at the termination of the Dicumarol test period (see below), the failure was considerably improved. The etiological and anatomical classification of the heart disease encompassed the common types. Cases of rheumatic heart disease with predominant left-sided valvular lesions, and cases of hypertensive and arteriosclerotic heart disease with and without previous myocardial

infarction, were included. Some patients had ectopic rhythms and most were afebrile. All were at strict bed rest under treatment with the usual medications and techniques including digitalis, mercurial and acidifying diuretics, xanthine derivatives and various sedatives. The use of salicylates was interdicted prior to or during the testing. The usual low-sodium ward hospital diet was administered but because of serious illness some of the patients may not have eaten satisfactorily. This point was not followed in the investigation. The overall nutritional status of the patients was not optimal and was probably lower (as a result of their illness) than that of most ward hospital patients. Nevertheless, as mentioned, they had recently been ambulatory and were in no sense in a state of cardiac cachexia.

In order to interpret accurately the hypoprothrombinemic effect of Dicumarol in the above group, we studied 48 control individuals who did not have any cardiac disease. Included were interns, nurses and orderlies of the hospital staff of average age less than that of the cardiacs and a group of patients convalescent from a variety of disorders not affecting the liver or the kidneys, in whom normal responses to Dicumarol could be anticipated. Both series, control and cardiac, were studied concurrently.

All of the test cases were examined by one of us and followed daily while being studied. Immediately after obtaining the first blood specimen, each patient or control was given a single dose of 150 mg. of Dicumarol orally. On each of the succeeding 3 days an additional specimen was drawn. Within 1 hour of the taking of the bloods, they were placed in a refrigerator where they remained until the prothrombin test was performed (usually 4 to 6 hours). On each day that tests were done, 1 or 2 normal individuals, who had not received Dicumarol, submitted blood for prothrombin determinations, and in all instances the prothrombin times of the patients and controls were compared with the normals. The response of each patient and control to the standardized dose of Dicumarol, therefore, was determined by 4 prothrombin tests at daily intervals, 1 test before and 3 after the drug had been given.

Because of the use of a minimally effective dose of Dicumarol in this study, it was necessary to make the prothrombin tests with 10% plasma. The Quick method as modified by Rosenfield and Tuft<sup>6</sup> was followed, using test plasma diluted with 9 parts of prothrombin-free plasma ( $\text{BaSO}_4$ ). Rabbit brain dehydrated with acetone (Difco) was the source of thromboplastin. The average of

3 such determinations on each specimen was taken as the prothrombin time. In addition, the prothrombin time of the undiluted plasma was also found. Even in cardiacs with severe failure the prothrombin time of undiluted plasma was hardly affected by the administration of 150 mg. of Dicumarol. This was in marked contradistinction to the effect on the 10% plasma prothrombin time (see results). All the tests were done by one of the authors.

In tabulating the results, the prothrombin time of the 1 or 2 normals was taken as the base line for the tests of that day. With undiluted plasma, this averaged 15 seconds and with 10% plasma, 24 seconds. The determinations of the controls and patients were charted as the number of seconds above (+) or below (−) [almost always the former] this value. The 4 days' testing in any instance was charted as a curve which represented the number of seconds on each of these days that the patient or control differed from its normal.

The detailed analyses of the data were performed with the results of the 10% plasma tests. For the purposes of statistical analysis and to present the results in compact form, the prothrombin curve of each cardiac patient and control was reduced to a single figure. This was derived by noting that test which, after the administration of Dicumarol, showed the maximal prolongation of the prothrombin time above the normal for that day. This was almost always the test performed 24 hours after the drug had been taken. This figure was further modified to the number of seconds above the normal or the pre-Dicumarol level for that patient; whichever was less. In some instances the number so obtained was the same as prior to modification (the patient's pre-Dicumarol prothrombin time was the same as the normal) but in many it was reduced, especially in the cardiacs. This is explained by the fact that in a considerable number of the latter the initial prothrombin time was above normal. The overall effect of the correction was to lower the figure for prolongation of the prothrombin time in the cardiacs.

Because of the procedure followed in performing a test of normal plasma and having the results of multiple tests on each cardiac patient, it was not considered advisable to deduce the concentration of prothrombin from the prothrombin time on a dilution curve. That such a procedure would not have affected the results or conclusions was shown by the calculation that the mean minimal concentration of prothrombin after 150 mg. of Dicumarol was 95% in the normals, 79%



in those cardiac patients with mild to absent failure, and 64% in those with moderate to severe failure.

**Results. PROLONGATION OF THE PROTHROMBIN TIME.** Fig. 1 shows the maximal prolongation of the 10% plasma prothrombin time induced by a single dose of 150 mg. of Dicumarol in control individuals and Fig. 2 shows the effect of the same dose in the cardiac patients.

Inspection of the bar diagrams reveals a greater prolongation of the prothrombin time in the cardiacs, but this applied only to those in moderate to severe right heart failure. Of the cardiacs in severe failure, 77% showed a prolongation of more than 6 seconds, whereas only 13% of the controls and 11% of the cardiacs in mild failure showed such an effect. For the determinations summarized in Table 1, those

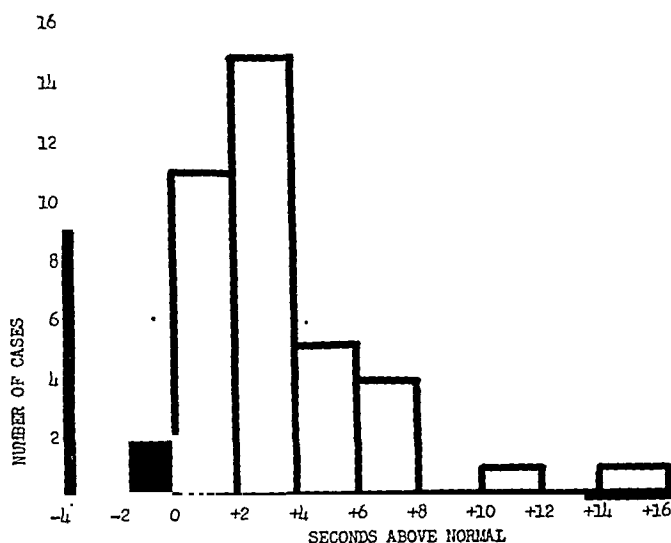


Fig. 1. Maximal prolongation of 10% plasma prothrombin time after 150 mg. Dicumarol in controls.

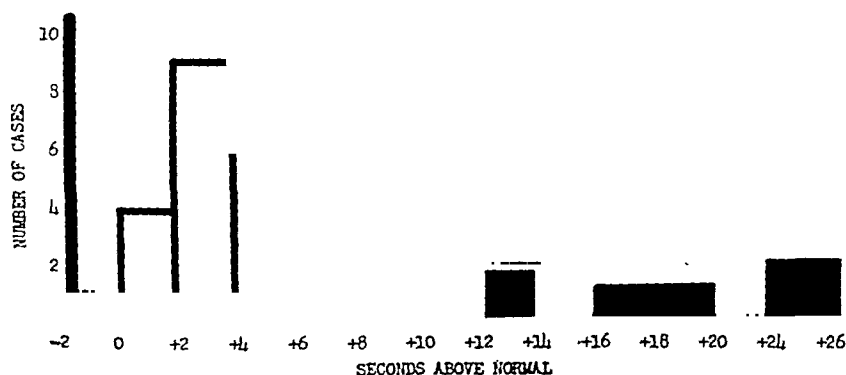


Fig. 2. Same as Fig. 1 in cardiac patients.  
Open bars = absent and mild right heart failure.  
Blacked bars = moderate and severe right heart failure.

cases in which the 10% plasma prothrombin times after Dicumarol were less than their pre-Dicumarol figures (negative values in Fig. 1 and Fig. 2) were regarded as showing no effect from Dicumarol. This simplification had relatively little influence upon the statistical constants and in the tests for significance.

TABLE 1. STATISTICAL CONSTANTS OF THE PROLONGATION OF THE PROTHROMBIN TIME.

|                            | CARDIAC FAILURE |              |              |
|----------------------------|-----------------|--------------|--------------|
|                            | Controls        | Mod. to Sev. | Abs. to Mild |
| Mean                       | 2.4             | 9.7          | 3.8          |
| Standard Deviation         | 3.1             | 7.4          | 3.5          |
| Standard Error of the Mean | 0.4             | 1.8          | 0.8          |

(the observed difference was 4 times the standard error); in all the cardiac failures the difference was of less significance (the observed difference was 2 times the standard error); in those with absent to mild failure the observed difference was not significant; the difference between the absent to mild and moderate to severe failures was 3 times the standard error and was significant.

In addition to the examination of the maximal prolongations, other subsidiary characteristics of the response to Dicumarol were noted:

1. The prothrombin time of 10% plasma prior to the administration of Dicumarol was 2.4 seconds higher in

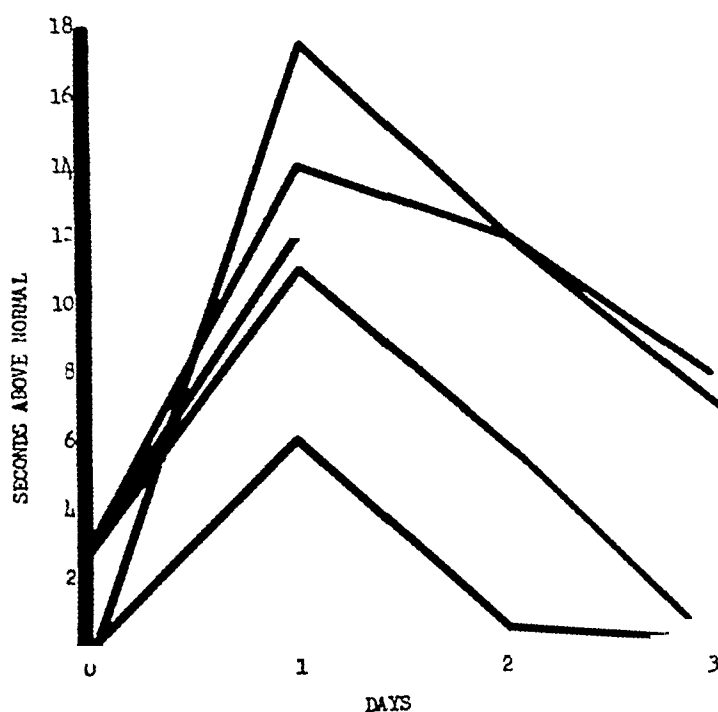


Fig. 3. 10% plasma prothrombin time curves of 5 cardiacs in moderate to severe failure. 150 mg. Dicumarol given on 0 day.

The standard error of the difference between the means of the controls and the other groups was 1.8 for the moderate to severe failures, 1.0 for the absent to mild failures, and 1.2 for all the cardiac failures. This difference in the case of the moderate to severe failures was highly significant

the cardiacs than in the controls. The time of onset of drug action could not be compared in the 2 groups because after 24 hours (2nd test) almost all controls or patients who were to show an effect from the Dicumarol, already exhibited a hypoprothrombinemia. Examinations of the blood at shorter

intervals after the administration of the drug would be necessary for this determination.

2. In assessing the intensity of action of Dicumarol, the duration of its hypoprothrombinemic effect was examined. In the controls, after the 2nd test there was a definite tendency for a rapid return of the prothrombin time to the initial level. In the cardiacs, especially those in more advanced decompensation, there was a more gradual fall, though at the time of the last test the curve had usually returned close to the initial value.

Fig. 3 shows the prothrombin curves of 5 cardiacs in moderate to severe failure, and Fig. 4 those of 5 control

administration of Dicumarol to cardiac patients . . . must be done with caution."

However, they did not mention the presence or absence of cardiac decompensation. Wishart and Chapman<sup>8</sup> treated a group of patients with congestive heart failure with Dicumarol and noted that such patients required a smaller dose of Dicumarol than compensated patients. On the other hand Anderson and Hull<sup>1</sup> treated 61 patients with Dicumarol, many of whom had moderate to severe congestive heart failure. The response to this drug was of the same order of magnitude as could have been expected in other patients. While our determinations were carried out in a different manner from those quoted,

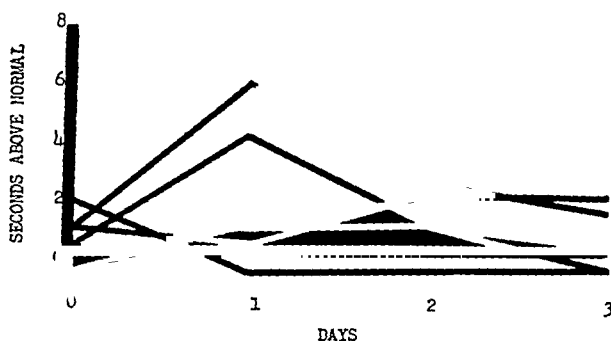


Fig. 4. Same as Fig. 3. Controls.

individuals. The more marked and prolonged effect of Dicumarol in the cardiacs is evident.

**Discussion.** These findings indicate that patients in moderate or severe right heart failure exhibit a greater hypoprothrombinemic response to a standard dose of Dicumarol than do normal individuals. Previous investigators have urged caution in the use of Dicumarol in such patients in order to avoid excessive hypoprothrombinemia. Cotlove and Vorzimer<sup>3</sup> treated 6 patients with heart disease and thromboembolic complications with Dicumarol and noted excessive reductions in the prothrombin. They stated "the

they are probably applicable to clinical practice and support the idea that smaller doses of Dicumarol should be used in the presence of heart failure than in its absence.

There is a variance of opinion regarding the prothrombin level of patients in heart failure. We found that with undiluted plasma there was no difference between controls and cardiacs, whereas, testing with 10% plasma, the prothrombin time of the cardiacs was 2.5 seconds greater. Cotlove and Vorzimer<sup>3</sup> found normal undiluted and 12.5% plasma prothrombin times in 13 patients with moderate or severe failure. Wishart and Chapman<sup>8</sup> report-

ed the average initial prothrombin concentration to be 62% of normal in their cardiacs, while Anderson and Hull<sup>1</sup> showed that 23 of 142 cases of cardiac failure had a prothrombin level much below normal; in 9 cases it was 30% or less of normal. Before Dicumarol is administered therapeutically to any patient, the prothrombin time should be determined. In the case of a patient in cardiac failure, a low level would be of great importance in the decision to use either a smaller dose of Dicumarol or another form of therapy. Administration of Dicumarol to a patient with a markedly reduced concentration of prothrombin is contraindicated.

While, in general, in our material the hypoprothrombinemia induced by Dicumarol was of much greater degree in severe as opposed to mild right heart failure, we could not satisfactorily correlate the magnitude of the response to the height of the venous pressure or the size of the liver within the group of severe failure. Others have assumed that both the initial hypoprothrombinemia and the excessive response to Dicumarol in these cases are due to impairment of liver function resulting from congestion. This is supported by previous observations of depressed liver function in congestive heart failure which were summarized by Lichtman<sup>5</sup> and the fact that hyper-

reaction to Dicumarol has been reported in some cases of cirrhosis of the liver<sup>7</sup>. The fact that in our cases the decompensation improved rapidly with a concomitant lessening of the effect of the Dicumarol on retesting, eliminates the possibility that organic changes (cirrhosis) could have been responsible for the observed effects. In addition to functional impairment of the liver, it is also possible that temporary derangement of renal function may play a role in this regard. That pre-renal deviation of fluids is a common occurrence in right heart failure has been known for a long time<sup>4</sup>. Administration of Dicumarol to animals with impaired kidney function results in extreme hypoprothrombinemia<sup>2</sup>.

Summary. 1. The hypoprothrombinemic effect of a single dose of 150 mg. of Dicumarol was determined in 48 control subjects and in 36 patients with varying degrees of right-sided cardiac failure.

2. Clinical and statistical analysis of the results showed an increased response in those cardiacs with moderate to severe failure.

3. When Dicumarol is administered to patients in cardiac failure for the treatment of thromboembolic conditions, doses smaller than those recommended for the average patient should be administered.

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# PROGRESS OF MEDICAL SCIENCE

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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## THE COLLAGEN DISEASES

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IN recent years the term "collagen diseases" has been introduced into medical terminology suggesting a relationship between several conditions that had previously been regarded as separate and unrelated disease entities. The association of these diseases has grown out of the belief by certain authors that the structural alterations are comparable, that the lesions involve the same types of tissues, and that the etiology is related in each instance to the hypersensitivity reaction. This paper is the result of an attempt to evaluate the merits of this association by a study of several cases of each type and a review of the pertinent literature.

First, by a discussion of the embryologic derivations of the tissues affected, we shall attempt to establish

the concept that these are not diseases of "collagen" but of the entire mesenchymal defense unit. Second, we shall consider the evidence of a common alteration of the physiology of this tissue unit on the basis of abnormal serum globulin levels. Third, we shall consider the cause which provokes the defense unit to activity. Fourth, we shall discuss the possible factors which condition the response of the defense organ; and, finally, we shall compare the clinical and pathological aspects of these diseases by a study of our own patients and of those reported in the literature.

**Concept of the Mesenchymal Derivatives as a Tissue Unit.** It is assumed, if the term "collagen diseases" is to be taken literally, that the common denominator of these diseases is a

lesion, structural or functional, seated in collagen. But collagen<sup>55</sup> is related chemically to hyalin, a homogeneous matrix produced by the active cartilage cell and to osteoid, the product of the osteoblast. This chemical relationship does not surprise us since these 3 cells, the fibroblast, the chondroblast, and the osteoblast, are all derivatives of the same stem, primitive mesenchyme, and in their early stages are morphologically indistinguishable. Indeed, there is considerable evidence<sup>72</sup> to support the hypothesis that the young forms of these cells may undergo transitions, one into the other, depending upon their environment and tissue evocators.

There is still another tissue type, again a mesenchymal derivative, which we believe plays an important role in the collagen diseases. This is the so-called reticulum or reticulo-endothelial system. By this term we mean that specific tissue substance of reticulated pattern that comprises a considerable part of lymph nodes, spleen and bone marrow and is represented in the liver in relatively large amounts by the Kupffer cells. We believe that a consideration of this particular mesenchymal derivative and its function is most essential to a discussion of the collagen diseases.

Since, in the collagen diseases there are consistent and fundamental changes in a minimum of two and often more of the above derivatives of mesenchyme and not in collagen alone, it seems profitable to examine this group from a phylogenetic point of view. In early embryonal life the mesenchyme exists as a body of immensely protean potentialities giving rise to the supportive, binding, and padding tissues of the body. But as the organism matures the mesenchyme itself becomes of less and less importance and its derivative cells, the fibroblast, chondroblast, reticulum,

muscle, and other types of less importance to this discussion, emerge and persist throughout postnatal life. Fig. 1 is a simple diagram illustrating the relationship of these cells.

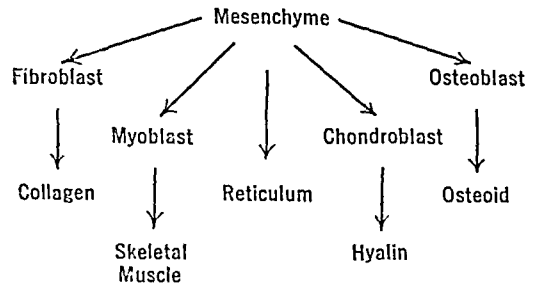


FIG. 1. Relationship of Mesenchymal Derivatives.

**Concept of a Common Functional Alteration.** One of the most important and primitive functions of the mesenchyme is that of defense. As it recedes with maturation, it bequeaths to its more differentiated offspring of cell types something of this same function. It is in the reticulum that we have a good example of a tissue adapted almost solely to this purpose. This defense function is achieved through both physical and chemical means. The lymph nodes are principally reticulum bodies strategically dispersed along lymph channels acting as mechanical filters for the particulate matter which might be injurious to the organism. The filtered matter is phagocytized by the littoral reticulum cells. This filter mechanism is probably one of the earliest of the reticulum functions. The reticulum also gives rise to motile histiocytes, monocytes, and granulocytes which may be dispatched to the scene of injury to actively phagocytize any particulate offending agent. Still further and still more important the reticulum and (probably) its derivatives are responsible for the formation of circulating antibodies, the immune globulins, which play a defense rôle in some yet unexplained manner.

The formation of globulin through

the action of the reticulum is not yet clearly understood. Globulin is apparently associated with the production of two cell types, each with densely chromatinized nuclei and cytoplasm peculiar to the cell, the lymphocyte and the plasma cell. Ehrich<sup>20</sup> and others<sup>41,31,52,18</sup> have indicated their belief that antibody production, and therefore gamma globulin production, is intrinsically bound with lymphocyte formation; others<sup>7,6</sup> believe that it is the plasma cell which plays the important role in this function<sup>6</sup>. It has been suggested in relation to the latter that the histiocyte may release certain principles of its cytoplasm as globulin and by this loss undergo a change in morphology becoming what we recognize as the plasma cell<sup>65</sup>. There is some evidence to support this hypothesis. The infiltration of plasmocytes occurs in inflammation about the time the antibody titer rises. High antibody titers have been found in accumulations of plasma cells<sup>22</sup>. Is it possible that both plasma cells and lymphocytes are concerned in globulin production, each responsible for its own particular protein fraction?

Since the fibroblast, chondroblast, and osteoblast are so closely related to the reticulum cell genetically, it seems reasonable to propose that they too inherit from the mesenchymal stem a defense function as well as one of repair. This character is probably expressed in the cytoplasmic constitution of the cell and, therefore, might be termed fixed or tissue immune substance in contradistinction to the circulating immune substance liberated by the reticulum and its derivatives. Such reasoning suggests that some change takes place within the constituents of the cytoplasm of the

mesenchymal derivative cells in response to an antigen. This substance might be considered analogous to the serum gamma globulin which is released by the reticulum. Assuming that the altered cytoplasm may undergo a characteristic degenerative change in the presence of the antigen, we delineate the tissue pattern of the various sensitivity responses on an embryologic basis. In support of this, Warren<sup>81</sup> found that labeled antigen in sensitized guinea pigs was found in the edematous peribronchial fibrous tissue in anaphylactic shock.

Thus, it follows that we may regard the entire system, the mesenchymal derivatives, as a tissue unit designed as an organ of defense which for the purposes of this discussion we may call the "defense unit." It is this defense unit upon which falls the whip of the noxious agents that cause the collagen diseases. We shall hereafter use this term to include the several tissues of varied morphology, indicating changes that include their function as well as their structure. We might diagram our defense unit and its components as in Fig. 2.

**The Agents That Provoke Defense Organ Activity.** The simplest example

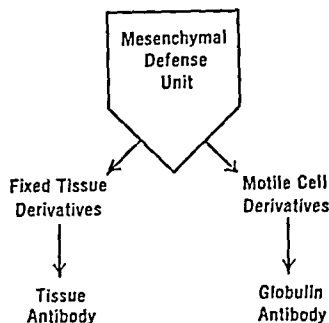


FIG. 2. Concept of a defense unit and its components.

\* Forman, Ehrich and Drabkin have very recently presented evidence ("Nucleic Acids and the Production of Antibody by Plasma Cells," *Fed. Proc.*, 8, 483, 1949) that inclines them to support this concept. See also an abstract in the Proceedings of the March meeting of the Phila. Physiol. Soc. (*Am. J. Med. Sci.*, 217, 710, 1949.) EDITOR.

of this defense mechanism is seen in the normal response of the body to an antigen, such as a foreign protein. An antibody is formed and released in the blood stream and as the antibody titer rises, the antigen level falls, presumably by some reaction resulting in antigen neutralization<sup>33</sup>. If the organism is subjected to further antigen contact in response to which the reticulum has already produced antibody, a hypersensitivity reaction may result. Such hypersensitivity reactions may take several forms according to Rich<sup>62</sup>, depending upon the route of entry of the antigen on first and subsequent contacts, the amount of antigen, the degree to which different sensitizable tissues become sensitized in different individuals or species, and the character of the sensitizing agent. Such reaction is commonly manifested by a lesion that embodies two separate processes. The first of these is a peculiar retrograde change which has been called fibrinoid degeneration. In its early stages it is distinct from other types of degeneration but if it proceeds to necrosis, it often loses its identity. When this process affects the walls of the capillaries, as it invariably does, it results in increased permeability. The second process manifested in these lesions is a proliferation of the reticulum derivatives. In the early stages it is usual to find proliferation of the endothelial lining cells and contiguous aggregations of histiocytes (macrophages)<sup>28</sup>, plasma cells, and lymphocytes. In the older lesions these cells are replaced by neutrophils and eosinophilic leukocytes as one might expect in consequence of the necrosis. In some of the collagen diseases<sup>44</sup> the fibrinoid degeneration predominates, in others the more dramatic feature is the proliferation, but in all there is at least an element of both.

We may regard the hypersensitivity reaction, then, as an abnormal activity

of the defense organ, characterized by a production of gamma globulin (antibodies) and alteration in the fixed mesenchymal tissue expressed in degeneration and proliferation.

**Concept of the Conditioning Factors.** There are other factors, however, that condition the reactions of the defense organ. These factors are so poorly understood that more than mere mention would be speculation. They may render the defense organ more or less vulnerable to the antigen provocator or they may cause a change in its products or its activity. One of these factors we may designate by the term constitution. Thus, the response may depend not only upon the stimulus but upon the individual and racial differences of the defense organ itself, "the stuff" out of which the mesenchyme and its derivatives are made. The constitutional factors would include not only the hereditary elements but also those concerned with environment, nutrition, and so on.

A second conditioning factor appears to be intimately related to the hormone secretions. We may designate this as the endocrine factor. That there is an inverse relationship between adrenal cortical activity and the amount of lymphoid tissue is fairly definitely established<sup>17,19,70,79</sup>. The autopsy pathologist is accustomed to finding large amounts of lymphoid and reticulum tissue in those conditions in which the adrenal cortex is hypogenetic or atrophied. It has long been known that the adrenal cortex is essential for the proper maintenance of the organism in the face of extremes of heat and cold, infections, and trauma<sup>68,67</sup>. The relationship between the adrenal cortical hormones and the production of the various globulin fractions of the plasma is not so clear. Some evidence suggests that the latter is inversely proportional to adrenal cortical activity. We know that in



Addison's disease with complete adrenal destruction or in adrenalectomy where there is a deficiency in all cortical hormones there is a fairly constant rise in serum globulin<sup>54,32,47</sup>. Conversely in Cushing's syndrome in which there is an increase in at least the "S" hormone, the globulin falls<sup>48</sup>. However, the work of White and Dougherty<sup>83,9</sup> may be cited to the contrary for they produced a rise in specific antibody (gamma globulin) by the injection of adrenal cortical hormone or pituitary adrenocorticotrophic hormone in animals. Mann *et al.*<sup>53</sup> observed no change in the serum proteins following the administration of adrenocorticotrophic hormone to a normal subject. Forsham<sup>25a</sup> reported a drop in the gamma globulin fraction of the serum proteins in one patient to whom adrenocorticotrophic hormone was given. Recently Hench and his associates<sup>35,36</sup> have shown in a small series of patients with rheumatoid arthritis and rheumatic fever that the elevated globulin returns to normal after administration of the Kendall Compound E. Since adrenal cortical secretion is stimulated by the pituitary adrenocorticotrophic hormone<sup>21,71</sup>, the pituitary, too, may play an important role in conditioning the defense organ. In addition, certain clinical aspects of the collagen diseases such as the sex incidence of lupus and rheumatoid arthritis suggest a relationship of the response of the defense organ to gonadal function. We have little knowledge whether it is an increase in secretions, a deficiency, or an imbalance, but we feel certain that these various hormones are important in conditioning the reaction of the defense unit. Experimental work is under way at present which we hope will illuminate some of the obscure corners of this aspect of the problem.

At present we may only hypothesize that the defense organ is provoked to

accelerated activity (normal or abnormal) by an antigen and that the nature of this activity is at least in part determined by the constitutional make-up of the organism and by hormone secretion. This complex reaction is illustrated in Fig. 3.

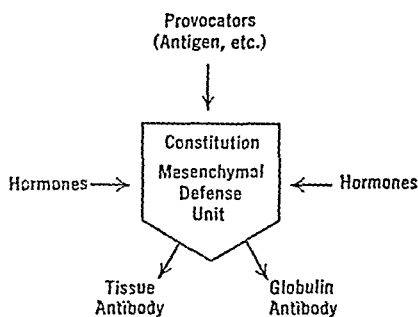


FIG. 3. Factors concerned in production of the defense reaction.

**A Comparison of the Clinical and Pathological Aspects of the Collagen Diseases.** This brings us to a consideration of the collagen diseases. Usually included in this category are periarteritis nodosa, rheumatic fever, and disseminated lupus erythematosus. We shall add serum sickness because of the clinical and experimental evidence of its similarity to periarteritis. With perhaps less justification we shall also include rheumatoid arthritis for reasons which will be given below. We believe that these 5 diseases have enough in common to warrant consideration as a group. With the exception of serum sickness they are all diseases of unknown etiology and the element of hypersensitivity, or at least altered sensitivity, reappears with varying degrees of importance in the other four. Though symptomatically they appear to be quite different entities, the predominant symptoms are all based on lesions of the mesenchymal derivatives whether they are in fibrous tissue, bone, cartilage, or muscle. In all there are disturbances in the globulin fraction of the blood

protein and the motile cells (infiltrating plasma cells and macrophages) of reticulum origin. In short, all of these conditions appear to be the result of a dysfunction and a degeneration and proliferation of the cells of what we have chosen to designate the defense unit. If the dissimilarities of these diseases can be explained on the basis of modifying influences upon this defense unit then the hypothesis that they belong to a group set apart from other diseases of mankind is strengthened. Such is the purpose of the following paragraphs.

*Serum Sickness.* In serum sickness there is no doubt as to the involvement of the mesenchymal unit. When the reaction is at its height there is generalized lymphadenopathy, a palpable spleen, swollen joints, and a high blood globulin<sup>51,29</sup>. The capillaries may be involved in permeability changes which manifest themselves as urticaria and albuminuria. In children there is at first a leucocytosis and later a leukopenia<sup>80</sup>; in adults, there is often no change in the blood picture except occasionally an eosinophilia<sup>72</sup>. The reaction is apparently purely and simply one of hypersensitivity. It follows 7 to 14 days after the injection of a foreign protein antigen to which the individual has been previously exposed and to which his mesenchymal defense unit has become sensitized. The disease is not fatal because the lesions are minimal and the reaction is of short duration (1 to 2 weeks). There is no specific age or sex predilection, although race may make a difference; negroes and American Indians appear to be less susceptible than whites<sup>52</sup>. There is a paucity of material concerning the histologic lesions of serum sickness in the human being for obvious reasons. Clark and Kaplan<sup>10</sup> reported two autopsied cases dying of pneumonia. Clinical evidence of serum sickness was present conse-

quent to serum therapy. They recorded cellular proliferation of the endothelial lining of the heart with subendothelial aggregations of histiocytes. There were perivascular foci of lymphocytic infiltration in the heart, liver, kidneys and adrenals. There was only slight evidence of degeneration in the form of fibrinoid change of the mesenchymal tissues. Rich<sup>58</sup> reported 5 cases of serum disease in which tissue was available for study. The findings for the most part were like those of the previous series except that fibrinoid degeneration was more conspicuous, resulting in lesions characteristic of those in early periarteritis nodosa.

Serum sickness can be produced experimentally by the injection of a foreign protein<sup>59</sup>. The lesions are not unlike those in human cases except that in addition Aschoff-like bodies and focal aggregations of monocytes or histiocytes have been described. It appears, then, that serum sickness is a hyperergic state in which symptoms arise from damage to vascular endothelial cells, histiocyte and lymphocyte proliferation, mild fibrinoid degeneration with eosinophilic leukocyte infiltration and increased capillary permeability.

*Periarteritis nodosa.* Periarteritis nodosa appears, in the light of present knowledge, to be an expression of a hypersensitive state. Although Rich<sup>59</sup> and others<sup>37</sup> have produced the lesion experimentally by sensitization of animals with foreign protein, clinically the relation to an antigen is not always so obvious. The disease has been described as arising after antipneumococcal serum and after sulfonamide therapy<sup>58</sup>. In more than 25% of the cases there is a history of a long-standing allergy such as asthma, hay fever, or hives<sup>84</sup>. In 10 to 14% there is an eosinophilia<sup>34</sup>. There may be an enlargement of the lymph nodes and spleen<sup>13</sup>. There may be swollen joints.

There is usually a leucocytosis and the serum globulin level occasionally has been found to be elevated in patients that have been tested<sup>40</sup>. As in serum sickness there appears to be no specific age group, no sex predominance, and so far as we know, no hereditary factor. The tissue alterations that are responsible for the symptoms are characterized in an early stage of their development by fibrinoid degeneration of the fibrous elements of the walls of arteries of small and intermediate size and a proliferation of the lining endotheliocytes. There are usually subendothelial and perivascular infiltrations of histiocytes, plasma cells and lymphocytes in varying numbers. Later the vessel wall undergoes necrosis and there is an infiltration with neutrophilic leucocytes. It is in this last stage that these lesions are most often examined so that the usual concept is one of necrosis and exudative reaction. If one compares the full blown lesions with those reported in serum sickness one might question the wisdom of considering these two diseases in the same category. However, it should be noted that some of the well developed lesions in serum sickness resemble those of early periarteritis, and the prenecrotic proliferative changes in the latter are like those in serum disease. This suggests that the one is a continuation or exaggeration of the other. There is also experimental evidence to support this thesis<sup>50</sup>. In the same animal species, the same antigen may produce the lesions of serum disease or, by a greater number of injections over a longer period of time, those of periarteritis. The clinical course of the two diseases supports this to a degree. Serum sickness is of relatively sudden onset, short duration, and rarely fatal. Periarteritis is more insidious in onset, its duration is measured in months and its outcome is usually fatal.

**RHEUMATIC FEVER.** Although in rheumatic fever there is considerable evidence that an altered sensitivity plays an important role, there are unquestionably other factors, such as infection and constitution, concerned. Clinically the disease is manifested by swollen joints and cardiac dysfunction. Pericarditis, pleuritis, pneumonitis, and peritonitis, all representing disease of the mesenchymal unit may occur. Although the lymph nodes may present microscopic changes, they are rarely enlarged, or at least not palpably so excepting those of the mesentery. Nor is the spleen palpable. There is a rise in serum globulin<sup>64,46,50</sup> and as in periarteritis there is often a leucocytosis. It is difficult to ignore the fact that attacks of rheumatic fever are often preceded by sore throat and that Swift<sup>75</sup> has shown the presence of pathologic amounts of antistreptolysin O in 90% of the cases. After inducing multiple successive focal group A streptococcal infections in rabbits, each caused by a serological type heterologous to those previously employed, lesions developed in the myocardium which Murphy and Swift<sup>56</sup> believe show a remarkable similarity to the pathognomonic lesions in human rheumatic fever. It is, therefore, assumed that it is the hemolytic streptococcus infection which is important in initiating the lesion of rheumatic fever.

The structural lesion of rheumatic fever is the Aschoff body. It is seen in its purest form in the interstitial tissues of the myocardium in relation to its arterioles but it may be found in a modified form in the subcutaneous rheumatic nodule, in the alveolar partitions of the lungs, in arterial walls and, indeed, in almost any of the mesenchymal tissues involved<sup>30,38,60</sup>. In its classic form it is not like the lesions of periarteritis nodosa and serum sickness, yet in 2 cases of fulminant rheumatic fever we have

seen lesions in the small arteries that are quite like those of early periarteritis nodosa, including the presence of fibrinoid degeneration and mononuclear cell infiltration. The work of Rich and Gregory<sup>61</sup> stands as the best experimental evidence that the lesions of these two diseases are similar. They produced what they interpreted as Aschoff bodies in animals sensitized to a foreign protein. Hopps and Wissler<sup>37</sup> and others have produced similar lesions. There are doubtless differences between the experimental lesions and those found in the human heart, but there has been an ever increasing tendency to accept these differences as reasonable variations in a type reaction despite the warnings of the purists.

Occasionally, acute rheumatic fever and periarteritis nodosa in young children may be difficult to differentiate clinically. There are, however, certain important dissimilarities between rheumatic fever and periarteritis nodosa and serum sickness. In rheumatic fever an age factor obtains, for the character of the disease changes as the patient matures<sup>85</sup>. Wilson<sup>86</sup> has stressed the fact that the susceptibility of the host is important and points out a strong hereditary tendency. Recently Hench<sup>36</sup> and his associates have reported the rapid clinical improvement of three cases of rheumatic fever with lowering of high serum globulins after the administration of the adrenal cortical hormone (Compound E). Thus we see that though rheumatic fever is a disease of the mesenchymal defense unit and though hypersensitivity may be an important element, the initiating factor of infection and the conditioning factors of age (endocrine ?) and constitution also play a part.

**RHEUMATOID ARTHRITIS.** Rheumatoid arthritis is a generalized systemic disease, the chief manifestation of which is painful swelling of the joints. In its

chronic form there is asthenia<sup>57</sup> and anemia<sup>23</sup>. There is usually elevation of the serum globulin<sup>16</sup>. Unlike the diseases discussed above, rheumatoid arthritis may present a leukopenia as the disease progresses<sup>23</sup>. In a rare adult type (Felty's syndrome) there may be an enlarged spleen and in the childhood manifestation (Still's disease) generalized lymphadenopathy and splenic enlargement are prominent as well as an elevated serum globulin<sup>76</sup>. In this disease the factor of specific hypersensitivity is not clinically or experimentally obvious. The role of infection has not been definitely determined<sup>34</sup>, although Sclater<sup>66</sup> reported that 12 to 21% of his cases were initiated by some type of infection and that foci of infection were found in 38%.

The symptoms are the result of degenerative and proliferative lesions in the fibrous tissue, hyaline cartilage, bone and periarticular muscle of the joints, all of which are mesenchymal derivatives. Indeed, careful examination will show changes in these elements that are characteristic, if not specific, in most of the organs<sup>4</sup>. Steiner and Chason<sup>73</sup> examined muscle biopsies from 27 cases of clinically typical rheumatoid arthritis. In 26 they found cellular aggregations of reticulum derivatives which they feel are highly specific for the disease. In 16 cases of lupus erythematosus they found similar though distinguishable muscle lesions in 6 and in 1, lesions which were identical with those in rheumatoid arthritis. In surveying a limited amount of material (biopsy material from 10 cases) we have been impressed by the pure and classical picture of fibrinoid degeneration. This is especially true in the rheumatic nodule and in the dense fibrous structure of the joint capsule. In the synovial membranes and subchondral tissues the cellular reaction in our cases was predominantly plasmacytic.

One might reasonably ask why rheumatoid arthritis is included in the collagen group. The reasons are summarized as follows: it is a disease of unknown etiology; it is a disease of mesenchymal derivatives; in the early stages the histological changes are characterized by fibrinoid degeneration and proliferation of the reticulum derivatives; there is an elevation of serum globulin suggesting a reticulum dysfunction. Infection or hypersensitivity to infection may play some precipitating role.

In rheumatoid arthritis as seen in the young patient there are important clinical similarities to rheumatic fever that first manifests itself in the second decade or later. In young children the cardiac manifestations of rheumatic fever are the prominent features, the involvement of joints being less prominent<sup>85</sup>. In adults the reverse is true and in this overlapping age group the two diseases may be difficult clinically to distinguish in the early stages<sup>14,24</sup>. The rheumatoid nodule may be indistinguishable from the nodule of rheumatic fever; there is a high incidence of rheumatic heart disease in rheumatoid arthritis<sup>63,5,24,87</sup>.

In this disease the endocrine factor becomes more manifest. As Pember-ton<sup>57</sup> has pointed out the asthenia, the hypotension, the abnormal sensitivity to heat, cold and exercise, and the elevation of the serum globulin suggest a hypofunction of the adrenal cortex either primary or secondary to hypofunction of the pituitary. There is also an association with ovarian function. In most series of cases there appears to be a predilection for females<sup>66,57</sup>. Remissions have been known to occur during pregnancy<sup>25,1</sup>. Joint manifestations may appear for the first time or may be exacerbated by the menopause<sup>66</sup> or following castration<sup>57</sup>. It must be admitted, however, that hormonal therapy had yielded disappoint-

ing results<sup>69</sup> until the work of Hensch<sup>35</sup>; 14 cases of moderately severe rheumatoid arthritis improved rapidly with the administration of the adrenal cortical hormone, Compound E; 2 others responded equally well to the administration of the adrenocorticotrophic hormone of the pituitary. Rheumatoid arthritis is said to be familial by both Cecil<sup>8</sup> and Pember-ton<sup>57</sup>.

To summarize, rheumatoid arthritis may be regarded as a systemic disease of the mesenchymal derivatives in which altered sensitivity and infection play still undefined roles as precipitating factors and in which the modifying factors of constitution and hormonal imbalance are probably concerned.

LUPUS ERYTHEMATOSUS. Finally we must consider disseminated lupus erythematosus. A study of our 9 cases, 7 of them autopsied, shows them to be typical of those found in the literature<sup>11,42</sup>. The patients were all females ranging from 12 to 41 years. The majority had generalized lymphadenopathy, a palpable spleen, and an enlarged liver. As clinical evidence of involvement of the mesenchymal derivatives there were serous effusions and capillary changes. In more than half the patients there was localized edema of the face and all of them showed evidence of kidney dysfunction which ranged from albuminuria to uremia. There was electrocardiographic evidence of myocardial damage in 9 patients. Pain and swelling of the joints were noted in 6. Although the eyegrounds were normal in 6 cases early in the course of the disease, in 4 edema and hemorrhage developed in the late stages. The typical skin lesion was present in all the cases at some time during the course of the disease and in most it involved other parts of the body as well as the face.

Evidence for a physiological disturbance of the mesenchymal defense unit

is seen in the disturbances in serum protein or in reactions attributed to such changes. There was an elevation of the serum globulin in all 9 cases. Severe auto-agglutination occurred in 2 patients and transfusion reactions that could not be attributed to mistyping or to the Rh factors were seen in 3 cases. The Wassermann reaction changed from negative to positive during the course of the disease in 1 patient and has been reported as fluctuating in 11 of 33 patients studied by Coburn<sup>12</sup>. In 4 of the 5 patients in whom a Congo red test was done it was positive. Teilum<sup>77</sup> has found what he calls an atypical amyloidosis in a high proportion of his cases of lupus. He believes these "amyloid" deposits are made up of abnormal globulin. Others<sup>78</sup> have reported a high incidence of amyloidosis in rheumatoid arthritis.

It is of interest that whereas a leucocytosis is common in periarteritis nodosa, in the early stages of rheumatic fever, and in rheumatoid arthritis, leukopenia, anemia, and thrombocytopenia are the rule in lupus erythematosus and in the late stages of rheumatoid arthritis. This might be due to a malfunction of the spleen, the "hypersplenism" of Dameshek<sup>15</sup>. In 4 of the 5 patients in whom the bone marrow was studied it was found to be normal or hyperplastic and there was, in these cases, no evidence of increased blood destruction so far as could be determined by fragility tests and serum bilirubin.

The structural lesions of lupus erythematosus have been adequately described by Libman and Sachs<sup>49</sup>, Baehr<sup>3</sup>, Klemperer<sup>43</sup>, and others. Essentially the lesion is one of fibrinoid degeneration of the mesenchymal derivatives. Occasionally the reaction in and about the small arteries may be accompanied by a proliferative reaction to produce a picture not

unlike that of periarteritis nodosa. Changes in the lymph nodes have been described by Fox and Rosahn<sup>26</sup> who believe them to be specific. We have only once found lymph node biopsy of great help diagnostically, but we have seen sections of a lymph node from a case of fulminant rheumatic fever that fitted well with their description. We believe that no pathologist would be willing to state that the cardiac lesions of lupus erythematosus are identical with those of rheumatic fever, yet there are certain common elements and within wide variations there is some overlapping. Concerning a comparison of the lesions of lupus and those of rheumatoid arthritis we believe there is too little recorded to warrant a conclusion.

Because of a degree of similarity of the lesions of lupus and those of the other collagen diseases we should consider what evidence there is for the factor of altered sensitivity in this disease. In our cases the following was found: in 1 case the disease flared up and the patient died within a month after the administration of 1 mg. of gold, in a second the condition was exacerbated by gold therapy, and in a third, agranulocytosis developed during treatment with sulfadiazine. Another patient had an eosinophilia as high as 12% for several weeks. Fatal or extreme reactions have been reported following the administration of tetanus antitoxin<sup>27</sup> and tuberculo-protein<sup>74</sup>. Ayvazian and Badger<sup>2</sup> reported death from lupus erythematosus in 3 nurses following Dick toxin and typhoid vaccine.

There is considerable evidence that infection may play a part in the development of the disease. Six of our patients described an infection as the precipitating event. These infections included a cellulitis of the knee, pharyngitis, pyogenic parotitis and an infected abortion. The factor of sul-

fonamide therapy which in itself might produce hypersensitivity makes incision hard to evaluate. In all of our cases minor but persistent infections were found early in the course of the disease: pharyngitis, sinusitis, mastoiditis, abscessed teeth, colitis. The terminal infections, empyema and staphylococcic septicaemia which were found at autopsy were probably the result of altered immunity and not important etiologically.

Concerning the endocrine factor in lupus erythematosus the evidence is confusing but it is apparently related in some manner. Almost all the cases are females in the active sex period<sup>11</sup>. Rose<sup>74</sup> reported a case in a male with an increased estrogen-androgen ratio. Coburn<sup>12</sup> reported testicular atrophy in one case in a male. In 2 of our cases, the disease was initiated by a long period of amenorrhea and in 2 it began in the postpartum period. There is also some evidence for hypofunction of the adrenal cortex. All of our patients complained of severe weakness and asthenia. Ultimately they became emaciated. It is known that the patient with lupus erythematosus reacts badly to extremes of heat and cold<sup>11</sup>. In 3 of our cases in which the blood chlorides were determined they were below normal. Coburn<sup>12</sup> reported a diffuse fibrosis of the cortex and lipid depletion in 3 of his cases. In 2 of our cases there was a definite degeneration of the adrenal cortex. At present we do not know whether the adrenal cortical hypofunction, if there is a hypofunction, is primary or secondary to pituitary dysfunction. Coburn<sup>12</sup> reported 1 case with focal necrosis in the pituitary. Although there is very little evidence in the literature<sup>28,39</sup> to suggest a hereditary or constitutional factor, 1 patient had a brother with "rheumatism."

Lupus erythematosus, then, is a disease of the mesenchyme and its deriva-

tives. Altered sensitivity and infection appear to play some, as yet undetermined, role in its etiology, and its character is probably modified by hormonal influences and perhaps by the constitutional make-up of the individual.

**Discussion.** We have presented the concept that certain of the cells arising from the primitive mesenchyme, including reticulum, and their products, globulin, collagen, and perhaps hyalin, osteoid, and muscle, play a role in the defensive as well as the reparative processes of the organism. When their responses are excessive or abnormal, certain diseases may result. We have reviewed some of the known facts, some of the experimental data and some of the theories of the mechanism and etiology of serum sickness, periarteritis nodosa, rheumatic fever, rheumatoid arthritis, and disseminated lupus erythematosus. The common factors of collagen degeneration, involvement of the blood vessels and the connective tissue of the heart, joints and other parts of the body, the presence of a common serosal lesion and the features of lymphadenopathy and splenic enlargement in addition to a rise in serum globulin suggest that these diseases are all abnormal reactions of the above mentioned mesenchymal defense unit. It has seemed to us that there are certain similarities between one and another, but as we progress through the series they show ever widening variations. To be more explicit, serum disease and periarteritis nodosa are very much alike at one end of the series with hypersensitivity playing a predominant rôle. At the other end rheumatoid arthritis and lupus erythematosus show some striking similarities but the factor of sensitivity is not so evident. Here there appears to be an abnormal function of the defense unit which differs from that which is found in serum sickness

and periarteritis nodosa and in which hypersensitivity apparently plays a small rôle. In the middle of the series is rheumatic fever. In the fulminant type of rheumatic fever in young children, the disease bears a resemblance to those on the left, particularly periarteritis nodosa; in the attenuated type in adults it tends to simulate the diseases on the right, especially rheumatoid arthritis. Regarded in the above order there are striking similarities of contiguous entities and striking differences between the diseases at either end of the series.

Whereas excessive or abnormal defense unit activity may be the basic disturbance in all these collagen diseases there are certain other modifying factors such as hormonal influence and constitution which also cause variation in the clinical and morphological characteristics. We agree with Klempner<sup>15</sup> that all these similarities are not specific enough for us to make the sweeping assumption that all the collagen diseases are simply a variety of manifestations of the same disease process with a single etiology. There are doubtless other factors, still undisclosed, that will explain differences in these conditions.

And lastly, although we have considered 5 entities under the heading of "collagen diseases," we do not mean to define its limitations so precisely.

Actually there seems to be much evidence that scleroderma and dermatomyositis also belong in this category. Also there is much about the lesions of glomerulonephritis and malignant hypertension that suggests a relationship.

**Summary.** We have suggested the idea that the collagen diseases affect not only the fibrous connective tissue but all the derivatives of the primitive mesenchyme: connective tissue, reticulum, cartilage, bone and muscle. We have proposed that the mesenchyme is a primitive organ of defense and it is not difficult for us to imagine a similar although less frank activity in its related tissue types. It follows that all of these tissues might be injured if the defense mechanism (immune reaction) became altered. We see the evidence of this abnormal antigen response in the reticulum and its product, globulin. The same abnormal response in related tissue types might conceivably produce the peculiar reactions, fibrinoid degeneration and reticulum derivative proliferation, that characterize the lesions in fixed tissue. The variation in clinical and pathological expression of these diseases might be accounted for on the basis of modifying factors of which constitution and the endocrine hormones appear to be of importance.

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# PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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## TEN YEARS IN THE EPIDEMIOLOGY OF MUMPS

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THE epidemiology of mumps<sup>43</sup> was selected in 1940 as a subject for this series of reviews principally for two reasons. In the first place a World War had just broken, with every indication that the United States would soon be involved. To the military surgeon, mumps is no passing indisposition of benign course but ranks with many of the more formidable diseases because of its frequent appearance in epidemic proportions, because of the high non-effective rate among Army personnel brought about by the long indisposition, and because in young adults the associated manifestations of epidemic parotitis lead to a clinical course considerably more serious than when mumps is a disease of childhood. The second consideration was that the specific mumps virus had recently been demonstrated by Johnson and Goodpasture<sup>57a</sup>, bringing promise of notable additions to knowledge of etiology, biologic nature and the mode of origin of mumps. There was the additional suggestion of more

effective measures for clinical recognition, especially of the more unusual forms of mumps, of improved methods of medical management, and of better control of the disease as it effects groups of people.

World War II has passed into history, so that it is now possible to appraise the behavior of mumps during the war years and to compare the experience of modern armies with what happened in former times. The record is good. Equally satisfying is the progress that has been made during the past 10 years in what is known about mumps as a clinical and biological entity.

Knowledge of mumps has developed within 3 periods. The first was concerned chiefly with the study of frank epidemics, and established both the communicability of the condition and its wide distribution. Hirsch's<sup>53</sup> collection of some 150 epidemics, occurring between 1714 and 1859, showed the disease to be prevalent from Iceland to Egypt, and from Alaska to

Polynesia. Accumulated evidence from outbreaks in the first half of the 19th century demonstrated another epidemiologic feature of mumps, its predilection for prisons, orphanages, boarding schools, garrisons, and ships. The second general advance was concerned with better definition of the clinical features of mumps, credit for which goes in large part to a brilliant line of French army surgeons. The third era was initiated with the production of mumps experimentally and the recognition of the specific infectious agent. The reader is referred to the earlier review<sup>43</sup> for an account of epidemiological interests up to 1940. The present discussion is of the extensive developments since then.

**Laboratory Aids to Epidemiological Study.** Epidemiology invariably profits from specific laboratory procedures. Knowledge of the virus is turned to use as an indicator of the people at risk and how they react. With more certain and regular diagnosis of the individual case, the principles and the generalizations on mass behavior become better defined, for they depend on the reliability of the basic data. The scope of modern field investigation is likewise greatly enlarged by incorporating the simpler laboratory procedures into field studies, and by applying methods of greater complexity in base laboratories to materials collected in the field.

The fundamental contributions of Johnson and Goodpasture<sup>57a,b,c</sup> left no doubt of the viral nature of mumps, but the technics for demonstration of the infectious agent and of immunity reactions in the human host were scarcely such as to be readily applied either in clinical diagnosis, or in studies in the field. Recent years have seen a variety of methods developed<sup>24</sup> by which the virus may be isolated from the lesions of the disease and by which the susceptibility or immunity

of a person to mumps infection may be determined with reasonable certainty. A number have been brought to such perfection that they are now incorporated in the ordinary activities of laboratories of state and other health departments.

*Complement Fixation Test.* This was the first serologic reaction to be adapted successfully to the study of mumps. Using infected parotid gland of the rhesus monkey<sup>57a</sup> as antigen, Enders and Cohen<sup>29</sup> in 1942 demonstrated a specific mumps antibody to be regularly present in serums of man and monkey convalescent from mumps<sup>31</sup>. In recent years the infected embryonated hen egg has come to be the more common source of antigen<sup>44b</sup>. The chick embryo infected with mumps virus also has been shown<sup>49a</sup> to contain 2 antigenically distinct components, separable by high speed centrifugation and differentiated by serum absorption technics. One is closely linked with the virus and found predominantly in the allantoic and amniotic fluids; it is designated V-antigen. The other is the soluble S-antigen, mainly present in infected tissues, the amniotic and allantoic membranes. Human serums from mumps patients<sup>48</sup> react in varying degree with S and V preparations, antibodies against the S substance appearing earlier than those for the V-antigen, but anti-V substance remains measurable for longer periods.

*Inhibition of Hemagglutination.* Amniotic fluid of mumps-infected chick embryos was demonstrated by Levens and Enders<sup>67</sup> to cause a specific hemagglutination, of fowl red cells. The hemagglutinin is also present in the yolk sac<sup>10</sup> and allantoic fluid<sup>15b</sup>. Some few other viruses<sup>36</sup>, as well as undetermined factors within the egg itself<sup>13,22</sup>, also give rise to agglutination of erythrocytes, indistinguishable from that brought about by the fluid from embryonated eggs infected with the mumps virus.

The specific nature of the hemagglutinin becomes apparent when its activity is inhibited by serum from patients or animals convalescent from mumps. This test for inhibition of hemagglutination, as recently modified by Robbins *et al.*<sup>84</sup>, has practical value by reason of its simplicity<sup>9a</sup>. A series of comparative tests with the complement fixation reaction show the two methods to be equally reliable. The previously noted non-specific reactions sometimes evidenced by serums of patients with early mumps and those from normal persons<sup>36</sup>, as well as other factors<sup>40b</sup> are no longer a practical consideration with the technique now used.

*Virus Neutralization Test.* The presence of virus neutralizing antibodies<sup>57a</sup> in the serums of animals recovered from experimental mumps infection was first demonstrated by inoculating test animals with serum-virus mixtures. Serums from patients convalescent from mumps also contain these antibodies, demonstrable either by test of serum-virus mixtures in the monkey<sup>31</sup> or in eggs<sup>44b</sup>. Although no clear correlation has been demonstrated between the amount of neutralizing antibody and the complement fixing antibody in a serum, both are ordinarily present<sup>44c</sup>.

Leymaster and Ward<sup>60b</sup> have further developed the virus neutralization test in eggs by using hemagglutination as an indicator of virus multiplication. The method is similar to that commonly used for influenza, except complement<sup>60c</sup> is necessary, to be provided by addition, or through use of fresh serum or serum frozen at low temperatures. The usefulness of the test in estimating mumps antibody levels, and presumptively for separating immune from non-immune persons, has not yet been established under field conditions.

*Agglutination of Human Red Cells*

*by Mumps Immune Serums.* Burnet<sup>15b</sup> treated human red cells of Group O with amniotic fluid from the mumps infected hen egg, removed the virus by elution, and obtained specific high titer agglutination of the cells with serums from patients convalescent from mumps. The demonstrated antibody response paralleled that shown by inhibition of hemagglutination tests, but the titers were higher. The virus itself or an antigenically active derivative was believed responsible for sensitizing the cells to the agglutinative action of antibodies. This method of determining and measuring antibodies has not had field trial in this country.

*Skin Sensitivity to Mumps Virus and Its Products.* Heat inactivated parotid gland from the experimentally infected monkey<sup>30</sup> and various tissues and fluids from the mumps infected embryonated egg<sup>44b</sup> have the capacity of inducing a mild, inflammatory, tuberculin-type reaction of the skin in persons previously infected with the virus of mumps. The test dose is 0.1 ml., injected intracutaneously; and similarly for the control, material for which is from uninfected tissues of a corresponding source. An erythema with a mean diameter greater than 10 mm. when observed at 48 hours is interpreted as a positive reaction, and indicative of an immunity to mumps providing the control test is negative. A varying degree of induration of the skin is usual. Non-specific reactions to the control material are uncommon. Experience has shown the test to be reliable within an error of 10%, using monkey materials under the conditions noted. Information about materials prepared from the egg is less extensive and less definite.

*Isolation and Cultivation of Mumps Virus.* Although the experiments of Johnson and Goodpasture<sup>57b</sup> had been repeated by at least 2 groups of inves-

tigators, one in England<sup>35</sup> and the other in France<sup>66a,b,c</sup>, the demonstration of the mumps virus by means of the parotid gland of infected monkeys remained in 1940 little more than a rarely practiced experimental procedure. Since then its use has been greatly extended, and was the starting point in the studies by American<sup>29</sup> and Australian<sup>93</sup> investigators which have so enlarged the knowledge of mumps. A mumps meningo-encephalitis was shown to follow intracerebral injection of infected mumps material<sup>65</sup>, with no associated parotitis<sup>93</sup>. Swann and Mawson<sup>93</sup> also produced parotitis in the monkey by intravenous injection of suitable materials.

A distinct advance was made when Habel<sup>44b</sup> and then Levens and Enders<sup>67</sup> successfully cultivated monkey adapted mumps virus in the developing hen egg, thus providing a readily available and inexpensive experimental animal. It was not long before Beveridge, Lind and Anderson<sup>10</sup> turned this method to direct isolation of mumps virus from the saliva of patients with mumps, Henle and McDougall<sup>51</sup> from cerebrospinal fluid of mumps meningo-encephalitis, and Kilham<sup>60a</sup> from the blood. Infected materials from man and experimental animals are readily propagated in the inoculated egg, when introduced into the yolk sac<sup>67</sup>, to the best advantage by the amniotic route<sup>69a</sup> and also by allantoic<sup>10</sup> and chorio-allantoic routes although definite lesions of the membrane are not produced<sup>67,85</sup>. The injection of polysaccharide prevents virus growth<sup>40a</sup>. Egg adapted strains multiply actively in tissue cultures<sup>99</sup> consisting of fragments of amniotic membrane of the chick, suspended in a mixture of ox serum ultra-filtrate and balanced salt solution, this being a far less complex medium than the chick embryo. Under all circumstances, the identification of an isolated virus as

mumps virus is accomplished by its specific reaction to the inhibition of hemagglutination and complement fixation tests.

*Serum Amylase in Mumps.* An elevation of serum amylase levels<sup>76</sup> is a regular accompaniment<sup>1,105</sup> of mumps infection, expressing a curve of excess values over normal<sup>104</sup> that tends to parallel the evolution and decline of clinical parotitis<sup>16</sup>, so that a well marked elevation is nearly always present in the first week, is less by the end of the second week and by the fourth week serum amylase above normal values exists for no more than 28% of patients. Lacking facilities for more precise determination of the activities of the mumps virus, this clinical-pathological test contributes to identification of obscure swellings about the jaw or instances where swelling has disappeared.

*The Nature of the Virus.* Much other information has accumulated about the virus of mumps; less striking, to be sure, than that concerned with its activities in the animal host, but potentially significant in a better understanding of its biological nature, and in the development of methods for improved prevention and control. What follows pertains to egg adapted virus.

The mumps virus has a particle size, as determined by Enders<sup>28f</sup> of 90 to 135m $\mu$ , which is within the range of the influenza virus. The observations of Weil *et al.*<sup>98a,b</sup> and of Habel<sup>44b</sup>, using different methods, suggest it to be about 190m $\mu$ , or even larger. Although infectivity of the virus is well retained by storage in the carbon dioxide ice box, it is lost within 4 days at room temperature<sup>24</sup>. Formalin in concentrations of 0.2% destroys infective power within 24 hours at 4° C., as does treatment with 1.5 volumes of ether for 30 minutes at 4° C. and exposure to intense ultraviolet radiation for 0.28 seconds. Neither penicillin nor strep-

tomycin<sup>97</sup>, separately or combined, cause demonstrable inhibition of growth of mumps virus *in vitro* or *in vivo*.

Kilham, Jungherr and Luginbuhl<sup>58,61</sup> have advanced a hypothesis that mumps virus and the virus of Newcastle disease of poultry may be biologically related. One-half of a series of patients convalescent from mumps showed a rise of neutralizing antibodies against Newcastle virus, and a nearly equal number an increase of antihemagglutinins. The 2 viruses not only agglutinate hen erythrocytes but Kilham<sup>60b</sup> has described a hemolysin associated with Newcastle virus similar in properties to that described by Morgan, Enders and Wadley<sup>73</sup> for the mumps virus. This coincides with the earlier suggestion of Burnet<sup>15a</sup> that mumps and certain other viruses are derived from a common ancestral form.

No evidence has suggested that different types<sup>9a</sup> of mumps virus exist, a matter of considerable importance in immunity and in control measures. Intracerebral inoculation of mice with mumps virus interferes<sup>96</sup> with proliferation of the virus of western equine encephalomyelitis.

The material gains in the past 10 years in knowledge of the infectious agent of mumps and in means for recognizing and measuring its activities in the human and experimental host, leave the clear implication that much has become known of better ways for defining the clinical disease, for judging its mass effect on groups of people, and presumably for a better understanding of the value and limitations of commonly used measures for prevention and control. These several matters will be considered in order.

**Laboratory Methods in Clinical Diagnosis.** Few of the communicable diseases present less difficulty in precise recognition by clinical means than

does mumps, providing it appears in the classical form of acute parotitis. The trouble lies in the frequency of other localizations. If the sole manifestation is of the central nervous system, the involvement of a testicle or a pancreatitis, the suggestion of mumps often rests on evidence no more secure than a history of exposure, which is none too reliable except in family outbreaks. When these unusual forms of mumps infection are associated with parotitis, the assumption of a single process is reasonably taken although not absolute. The neurological manifestations with concurrent infection of the central nervous system and a salivary gland may or may not be mumps. Latent or subclinical mumps is, by definition, below the level of clinical observation and not to be recognized by bedside methods; and yet, of all the forms of mumps, it is the commonest aside from classical parotitis. Only laboratory procedure identifies this kind of mumps infection.

The inhibition of hemagglutination test for mumps infection, as now modified<sup>84</sup>, answers most needs for a specific diagnostic procedure. A four-fold or greater increase in antibody titer during the course of an acute infection marks it as of mumps origin. Two specimens of serum are necessary for the test, the first taken as soon as possible after onset, for antibody tends to appear promptly, and a second sample obtained after 14 to 21 days. The difference in antibody level between the 2 specimens may be sufficiently great to make the diagnosis definite within a week; it is almost always so by the end of the second week, although instances occur where the response is delayed to the third week. Serum antibodies not uncommonly attain a high level before the need for the test becomes apparent, particularly in mumps infection unassociated with parotitis<sup>59</sup> or in mumps meningo-

encephalitis subsequent to parotitis<sup>77</sup>. A significant increase in titer cannot ordinarily be expected in such circumstances; values well beyond observed maximal levels<sup>24</sup> for normals or acute phase infection may be taken presumptively as evidence of recent infection, but always with reservations.

The complement fixation test continues to be much used as a diagnostic procedure, although supplanted more and more by the simpler antihemagglutinin test. The virus neutralization test<sup>31,44b</sup> is less used than either of them. The skin test for hypersensitivity to mumps antigen, of chief use in immunity studies, can also serve as a diagnostic procedure for apparent or inapparent infection, where a known negative test is demonstrated to have changed to a positive reaction. A preceding skin test discounts the usefulness of complement fixation as a diagnostic aid because it frequently calls forth specific antibody, or leads to its increase if already present<sup>32</sup>.

The satisfaction that comes from isolation of the infectious agent in confirmation of a clinical diagnosis is not commonly experienced in mumps, because of the associated technical difficulties. Consequently, the attempt is ordinarily reserved for special situations or a particular need. Indirect diagnostic aid may be provided by increased serum amylase levels.

An improved knowledge of the nature of mumps, considering the disease broadly and biologically, would expectedly follow application of these newer diagnostic procedures to the less well defined clinical manifestations of the disease. The progress of the past 10 years will be examined.

**The Clinical Disease.** Some communicable diseases are so strictly limited in their disease producing activities that clinical behavior is completely predictable, such a disease being rabies in man. Others are of such protean

nature as to warrant the characterization Erasmus Darwin gave scarlet fever, that it could simulate anything from a flea bite to the plague.

Mumps has long been recognized as a good deal more than a simple disease of the parotid glands. The biologic gradient of infection is characterized by varying severity, and a complexity that includes an associated or independent involvement of the other salivary glands, the gonads, the pancreas, the central nervous system especially, and a number of other structures including those of the special senses. A matter of epidemiologic concern is whether or not latent infection exists, that is to say, inapparent or subclinical infection below the level of clinical recognition. This bears pertinently on an understanding of the disease as a mass phenomenon, and on projected methods for prevention and control.

*Latent Mumps Infection.* Practical experience in epidemics has suggested that latent infection is a factor in the spread of mumps virus<sup>41a</sup> and our earlier review<sup>43</sup> presented epidemiologic evidence in support of an hypothesis that the incidence of subclinical infection is large. Additional information continues to accumulate. Siegel and Camp<sup>88</sup> saw an epidemic in a mental institution in 1940, and 4 years later another, of 11 cases. Only children admitted after the first epidemic were involved in the second. While the attack rate in 1940 was high, it was not sufficient to permit the assumption that all susceptibles had been exhausted by clinical attack. The better explanation was that a number had been rendered immune through latent infection. That such latent immunization occurs has now been clearly demonstrated.

To establish the existence of latent infection in the human host, an acquired immunity must be demonstrated comparable to that which fol-



lows the usual form of the disease. Isolation and identification of the infectious agent greatly strengthens the proof. The method for demonstrating such an immunity was provided by Enders and Cohen<sup>29</sup> in 1942 with the complement fixation test. Positive reactions were soon observed<sup>30</sup> in the absence of clinical disease, bringing the direct suggestion of inapparent infection. This became more certain as increasing experience showed that a positive complement fixation test means previous infection<sup>74</sup>. With rare exceptions such latently infected persons were resistant to infection through natural exposure<sup>40b</sup>. Still better evidence came from observation of known negative reactors<sup>74</sup> who were exposed to mumps, contracted no demonstrable disease and yet developed complement fixing antibodies, clearly the result of latent infection. About all that could be asked by way of proof of latent infection was produced by Henle *et al.*<sup>50</sup> through observations on 15 volunteers exposed to mumps virus. Seven became ill, 4 with classical parotitis, and 8 remained well. All 15 showed similar antibody response, the sick indistinguishably from the well. Most significantly, mumps virus was isolated from 13 of the 15 persons exposed, without exception from those ill, and from 6 of the 8 well, with isolations from the well group corresponding in time to those for the clinically ill. The estimate of about one third of all mumps infections being latent, as judged by experimental results, is in close agreement with what was determined epidemiologically.

*Classical Parotitis.* For a disease which has maintained such clinical uniformity since the days of Hippocrates, it is unusual to find attention directed to an unemphasized physical finding, that of presternal edema. This clinical sign was noted by Radin<sup>59</sup> in

the first World War but has not gained entrance to standard texts. An edema of the tissues of the anterior wall of the thorax<sup>82</sup>, and sometimes of the abdomen<sup>7</sup>, is an occasional feature of parotitis and occurs more particularly with involvement of the submaxillary glands. When present, presternal edema tends to appear promptly after mumps becomes manifest<sup>17</sup>, and the cause<sup>39</sup> would seem to rest in obstruction of the lymphatics by the swollen salivary glands.

The aid to diagnosis provided by serologic tests and isolation of virus from the saliva, is the principal advance in ordinary mumps infection; the chief usefulness being the differentiation of ill-defined or atypical swellings in the region of the jaws.

*Mumps Meningo-encephalitis.* The clinical<sup>73</sup> and epidemiologic<sup>43</sup> evidence in support of an involvement of the central nervous system in mumps has been fully substantiated by the newer laboratory procedures. Mumps virus was first isolated from cerebrospinal fluid through monkey inoculation by Swann and Mawson<sup>83</sup> and through egg culture by Henle and McDougall<sup>51</sup>. Serologic methods, as used by Kane and Enders<sup>59</sup>, earlier provided a satisfactory method of recognition. The practical result has been a better understanding of a knotty clinical problem. Mumps meningo-encephalitis in the absence of parotitis can now be determined with certainty. Of equal importance, infections of the central nervous system, presumed to be of other nature, are now recognized as sometimes due to the mumps virus. In the summer of 1948, 6 of 17 patients in Boston with a clinical diagnosis of non-paralytic poliomyelitis were found by Kilham, Levens and Enders<sup>62</sup> to have mumps meningo-encephalitis. The observed frequency in this instance may be greater than usual, by reason of a state-wide epidemic of mumps

during the preceding spring, but the circumstance would appear sufficiently common to warrant examination of questionable non-paralytic poliomyelitis by serologic methods for mumps.

As for the disease itself, it has been shown to precede, accompany or follow parotid involvement<sup>14</sup>, and sometimes to occur as the only clinical manifestation of mumps<sup>62</sup>, to be included within the group of conditions termed aseptic meningitis<sup>27</sup>. It has a wide geographical distribution<sup>2,18,89</sup>.

The military experience of the recent war<sup>4</sup> again provided information about the frequency of mumps meningo-encephalitis in young adult populations. Of 100 consecutive admissions to hospital where lumbar puncture<sup>54</sup> was uniformly practiced, 33 patients had clinically determinable disease of the central nervous system although none were seriously ill. Ten others were judged to have subclinical infection by the number of cells in the cerebrospinal fluid, and 14 additional patients were considered borderline. A second similar series of 77 patients reported by Brown, Kirkland, and Hein<sup>14</sup> included 9 with clinical meningo-encephalitis, all mildly ill except one, with 26 in all having 10 or more leukocytes in the spinal fluid. The selected age group of young adults, at least under military conditions, is evidently susceptible to central nervous system involvement when invaded by mumps. A minor clinical reaction is characteristic, although some cases are severe. Latent mumps infection of the central nervous system is strongly suggested as being more frequent than generally appreciated. It is proved to exist by laboratory means.

The need of the moment is to determine quantitatively the range of clinical manifestations included within mumps meningo-encephalitis, and secondly, the frequency of this disease in a

general population. For example, there is indication that males<sup>60c</sup> are affected five times as frequently as females. It becomes apparent that slightly increased numbers of cells in the cerebrospinal fluid and a demonstrated general mumps infection by complement fixation or other serologic test does not suffice in recognition. The cell count is usually increased in frank cases of nervous involvement<sup>6,60c</sup>, but sometimes the cerebrospinal fluid may be virtually normal<sup>46</sup>. Conversely pleocytosis may or may not be accompanied by symptoms of meningeal irritation.

The necropsy report of Donohue<sup>25</sup> on mumps meningo-encephalitis is one of the few available. The basic lesion was a perivascular demyelination similar to that seen in post-infectious encephalitides, and essentially like two others of 10 fatal cases with autopsy, which were reviewed. The unsettled question is raised, whether the few fatal cases of mumps meningo-encephalitis represent extreme examples of the same process so commonly an accompaniment of mumps, or have to do with a post-infectious demyelinating type of infection. Mumps virus has not yet been isolated from a fatal case of meningo-encephalitis, but the method is available to settle this problem.

*Orchitis.* The experience of the second World War was in agreement with previous observations that mumps in the young adult under military conditions is frequently associated with a complicating orchitis, the reported incidence of 35% by Dermon and LeHew<sup>23</sup> being not unusual. Hook, Poole, and Friedewald<sup>55</sup> isolated mumps virus from the testicle of a patient with orchitis. The histopathological study of acute mumps orchitis by Gall<sup>37</sup> is especially informative. Opportunity was taken to remove bits of testicular tissue at the time of

orchidotomy for relief of pressure, with 75 such cases studied at times ranging from the first to the fifth day of disease and additionally one case with death on the eleventh day. Considerable variation was noted in the character and extent of lesions, but it appeared that a developmental trend could be detected. The lesions varied from those of an early edema and a scant perivascular lymphocytic exudate to conditions corresponding to diffuse lymphocytic infiltration of the interstitial tissues, with focal hemorrhage and pronounced destruction of germinal epithelium, associated with plugging of tubules by epithelial debris, fibrin and polymorphonuclear leukocytes. The intratubal lesion remained focal in most instances, but in a few every tubule in a given section was involved. Inflammation of testicular appendages and the epididymis was confined to connective tissue elements and with one exception was wholly lymphocytic. Epithelial elements of these structures were unaffected.

*Other Clinical Manifestations.* Of principal interest because of added evidence that mumps is a generalized infection<sup>12</sup>, are the data provided by Veghelyi<sup>25</sup> indicating that pancreatitis is not a rare component of mumps infection. The diagnosis becomes definite with modern laboratory aids. A patient at the Peter Bent Brigham Hospital, Boston, had acute pancreatitis as judged by signs, symptoms and a serum amylase test, but no parotitis. Further investigation<sup>26a</sup> showed the patient to have a rise of mumps complement fixing antibodies in convalescence.

Myocarditis<sup>51,101</sup> has been observed in a number of instances of mumps infection. Of 104 adult patients<sup>56</sup> with mumps, 157 gave evidence of myocarditis, usually from the fifth to the tenth day of illness, but mild and transitory and recognizable only by

electrocardiographic methods.

*Immunity.* That an attack of mumps usually confers a lifelong immunity rests on good clinical and epidemiologic evidence. Additional proof is had in the results of the experimentally induced disease in animals<sup>28d</sup>, since attempts at reinfection are without result. Occasionally, however, a firm, hard swelling is seen to follow within 3 days after reinoculation of immune animals with active virus. This is interpreted as a manifestation of hypersensitivity, because it appears more promptly than do the symptoms of infection, because of the difference in character of the swelling, and because of the shorter duration. The phenomenon suggests an explanation of some of the reported instances of second attacks of mumps in man. They are not wholly infrequent<sup>11</sup>. Many probably rest on an unreliable history but not all, for sometimes both attacks have been seen by the same observer<sup>23</sup>. A common circumstance is an absence of secondary cases among contacts<sup>63</sup>. The failure of Beveridge, Lind and Anderson<sup>10</sup> to isolate virus at the time of the second event has been a consistent experience in our laboratory. Through the interest of Dr. E. H. Place, opportunity was afforded to examine a number of patients with parotitis, usually indistinguishable from mumps and with a history of previous involvement of similar nature. One such patient had 5 attacks of parotitis in the course of a year, sometimes unilateral and sometimes bilateral, each subsiding in about a week. Thus far no presumed second attack of mumps has been substantiated either by virus isolation or serologic test.

Field trial<sup>32</sup> has confirmed the skin test originated by Enders<sup>50</sup> and the neutralization test of Habel<sup>14d</sup> as reliable means for determining the index of susceptibility of populations. Generally, the skin test is a more sensitive

indicator of past infection than the complement fixation reaction, and the most practicable as a field method<sup>28b</sup>. Judged by this test and the history of previous clinical mumps, about one third of all demonstrated mumps infections are latent in nature.

More direct evidence of latent infection and immunity is provided by a series of 78 persons intimately exposed to mumps<sup>74</sup>. All had a negative complement fixation test and none developed the disease, and yet 31% reacted positively when tested one month later, a clear indication of latent infection. The validity of the evidence depends, of course, on the complement fixation test being a reliable indicator of immunity. That has been fully proven<sup>74</sup> and repeatedly confirmed<sup>49b</sup>. Of 163 persons with a positive reaction, only one developed mumps after known exposure. Of 285 with a negative test, 56 contracted the disease. It is evident that not all persons with a negative immunity test will develop clinical mumps when exposed. In the first place, a goodly proportion will experience latent infections. Effective protective antibody may be present when complement fixing antibodies are absent or below a measurable level. That many persons are exposed a number of times before developing the disease is evidence that close contact and a goodly dose of the agent are necessary for infection.

The mechanism of immunity in mumps is not wholly defined. It is rather clearly associated with the production of specific immune bodies; but the complement fixing antibody is not to be inferred as the essential factor, although a good index of immunity. Neutralizing antibodies can usually be demonstrated when the complement fixation test is positive, but the titers of the two do not necessarily parallel each other.

**Pathogenesis of Mumps.** Using a

variety of evidence, epidemiologic, clinical, immunologic and experimental, an hypothesis<sup>43</sup> was stated in 1940 in explanation of the pathogenesis of mumps. It would appear that the portal of entry is by the nose and mouth, with lodgement of the mumps virus on the mucosal surfaces. An appreciable weight of evidence indicates mumps to be a general infection, probably of the blood stream, and not a strictly local disease. In the localizations that follow the general infection, the virus manifests a special predilection for glandular structures of which the parotid is most often the first affected. With multiple structures involved, swelling of the parotid usually precedes all others, but sometimes this sequence is disturbed with striking effect on the timing of the disease, so that the testes, the central nervous system or the pancreas may be first invaded.

Alternative explanations<sup>94</sup> that mumps is a strictly local disease with occasional complications, or that it is a primary disease of the central nervous system with secondary localization in the salivary glands or other structures, were deemed less likely as representing the usual course of mumps infection. The second explanation, originally advanced by Philibert<sup>78</sup> is not disposed of as easily as the first, despite its having received little support from the newer facts about mumps. Kilham<sup>60c</sup> was unable to demonstrate virus in spinal fluids of patients with parotitis and no symptoms referable to the central nervous system, using methods which were uniformly successful with clinically defined mumps meningo-encephalitis. Further work is justified.

Additional evidence has accumulated during the 10 year period under consideration to support the hypothesis first given, that mumps is a general infection, probably blood borne, with

subsequent selective secondary localization. Mumps virus has been isolated from the cerebrospinal fluid of meningo-encephalitis with sufficient frequency<sup>60c</sup> to establish a direct relationship between this condition and parotitis. The postulated blood invasion has been confirmed by isolation of the virus from the blood in early mumps<sup>60a</sup>, although more information is needed about the frequency with which that occurs, and whether it is a regular event or an occasional spilling over into the blood stream in the course of a heavy infection or a peculiar localization. Virus has been found in the infected testicle<sup>55</sup> and the presence of antibody in hydrocele fluid has been demonstrated by complement fixation techniques<sup>28a</sup>. The reported clinical recognition of mumps myocarditis and the estimated frequency of pancreatitis contribute evidence marking the disease mumps as a general infection. The solid immunity is strongly suggestive of blood stream invasion, for that is the usual event in diseases followed by permanent protection.

The short incubation period in monkey and in man, about eight days, when mumps virus is introduced directly into Stenson's duct, compared with 18 days when it is deposited on the mucus membranes of the upper respiratory tract, strongly suggests the latter to be the natural course of invasion.

Based on comparative studies of mumps virus, the influenza virus and the virus of Newcastle disease, and a demonstration of common properties. Burnet<sup>15a</sup> reasons that like the other agents, mumps virus multiplies in the superficial and epithelial cells of the respiratory tract or conjunctivae and causes initially a subclinical infection. This primary invasion produces enough virus to enter the blood and localize in the parotid or other organs. The parotid and other salivary glands are

thus looked upon as structures through which mumps virus is eliminated, rather than those by which it gains entrance.

Enders<sup>28d</sup> thinks of the inflammation and swelling of the parotid gland and of other organs in mumps infections, as the result of union of antigen and antibodies within the tissues. There is evidence to support such an hypothesis. Mumps antibodies are frequently demonstrable close to onset of the disease. This is not surprising, considering the incubation period averages 18 days. Furthermore, monkeys inoculated with mumps virus by way of Stenson's duct may have a considerable amount of virus present in the parotid gland 4 to 5 days later as evidenced by titers of complement fixing antigen. Swelling, however, is not generally present until a few days after that, when antibodies may be demonstrated for the first time. The reaction of the immune animal to reinjection is further evidence.

**Spread of the Virus.** Because of the advantage of looking upon communicable disease as an ecologic phenomenon<sup>42</sup>, the present discussion was initiated with the characteristics of the mumps virus and of the immunity reactions in the human host. The first requisite is to know the two components of the host-parasite relation and how that relationship expresses itself in terms of disease. It remains to examine the effect of environment; more particularly, the means by which agent and host are brought into contact and the results that follow, as illustrated by the mass behavior of mumps in communities of people.

*Period of Communicability.* Other than the innate characteristics of host and agent, which is the primary consideration, the frequency of a communicable disease is determined by the numbers and kinds of reservoirs of infection, by the time they remain active, and by the efficiency and vari-

ety of modes of transmission. Based on epidemiological evidence, the period of communicability of mumps has been judged to be 48 hours before appearance of the disease as a swelling of the salivary glands and until that swelling has subsided. The ability to isolate the virus by simple technical procedures has contributed more precise information.

Experimentally induced infection in children<sup>50</sup> shows the virus to be present in the saliva as early as 6 days before clinical mumps and commonly by the second day. In the course of the same observations Henle and co-workers<sup>50</sup> demonstrated the agent for as long as the fourth day of active disease, with Leymaster and Ward<sup>69a</sup> reporting successful isolation on the sixth day, and Kilham in a single instance on the ninth day. The period of communicability thus appears to be about 10 days, starting regularly before mumps can be recognized clinically and ending shortly after the appearance of swelling. Daily tests of saliva by Kilham showed the virus to be excreted continuously until it finally disappeared, rather than intermittently as otherwise suggested<sup>50</sup>.

Comparing epidemiologic experience with the results of virus isolation, the limit of 6 days before parotid swelling would appear a definite maximum. The accepted practice of considering communicability to have ceased with the subsidence of swelling should fit most situations, although epidemiologic evidence<sup>50</sup> suggests that the upper limit of 9 days as determined by virus isolation may occasionally be exceeded.

*Reservoirs of Infection.* Reservoirs of infection in mumps are limited to human beings. Epidemiologic methods have served to establish only the classical case of mumps as a certain source of infection, although atypical and latent infections have been strong-

ly suspected. Laboratory proof now shows that persons with latent infection also excrete the virus in the saliva over considerable periods and are capable of spreading the disease<sup>50</sup>. Those instances of mumps infection with manifestations limited to the central nervous system likewise show virus in the saliva<sup>60c</sup> and more particularly patients are known to have transmitted classical mumps to contacts<sup>27,56</sup>.

The conclusion to be drawn is that the actual community dosage, as judged by the number of reservoirs of infection, is greater by perhaps one third than indicated by the existing prevalence of ordinary parotitis as determined by survey sampling; and measurably greater than an estimate based on officially reported cases of salivary gland enlargement. The efficiency of reporting under good conditions lies between 10% and 20% of actual cases, and rarely exceeds 40% except in military practice, being somewhat better in epidemic than endemic times.

*Mode of Transmission.* The usual method of transmission is by direct contact and probably by droplet infection, with perhaps occasional instances where mumps results from early contact with an article recently contaminated with the saliva of a patient<sup>21</sup>. Normal monkeys in contact with infected animals are known to have developed resistance<sup>28d</sup>, presumably as a result of subclinical infection.

Clinically, there are no symptoms in mumps such as coughing or sneezing which would induce any large amount of droplet nuclei formation. Under most circumstances mumps is, therefore, not a true airborne disease<sup>44a</sup>. When it occurs at the same time as upper respiratory infections, Stallybrass<sup>91</sup> finds the disease to spread more rapidly and more widely than ordinarily, because of the increased

droplet formation due to concomitant sneezing and coughing.

**Endemicity and Epidemicity.** The problems in the epidemiology of mumps that most commonly attract attention, and therefore gain entrance to the medical literature, are those of military groups, of schools and other institutions where appreciable numbers of susceptibles have a common exposure. Mumps in urban civilian populations is a firmly established endemic disease, conforming to the

*Civilian.* Outbreaks of mumps under normal conditions are rarely explosive, ordinarily extend over a whole season and sometimes are still further prolonged. For example, the last Massachusetts epidemic started in the autumn of 1947, continued strongly active in 1948 and in the spring of 1949 was still well over normal incidence. The Illinois experience was similar. Judged by the average incidence for the 34 years of 1915-1948 that mumps has been reportable in

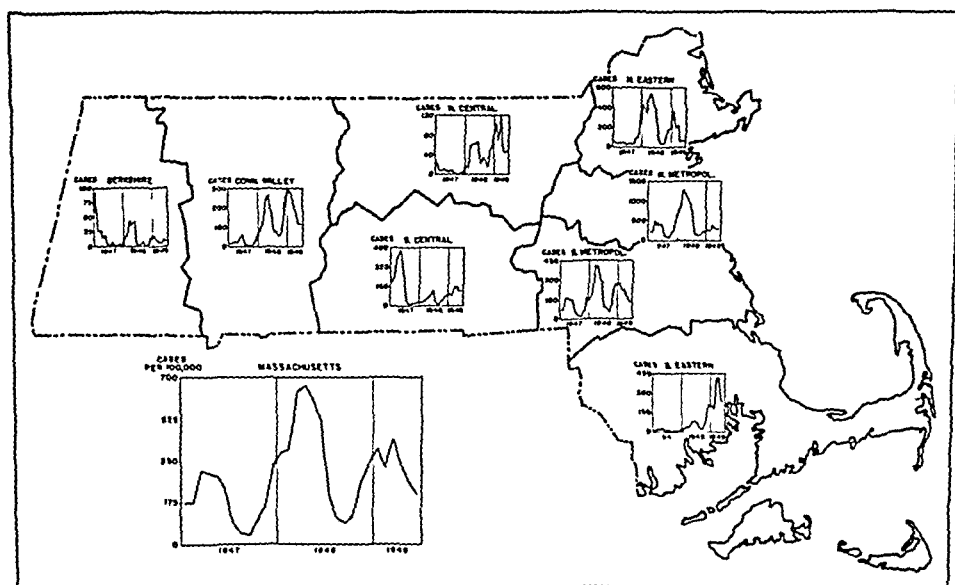


FIG. 1. Mumps, cases by months, Massachusetts Health Districts, and cases per 100,000 population, by months, Massachusetts, January 1, 1947, to June, 1949

Source: Div. of Communicable Diseases, Mass. Dept. of Pub Health.

general laws governing other infections peculiar to childhood<sup>17</sup>. A cyclic distribution is characteristic, with epidemics about every 7 or 8 years; Illinois<sup>18</sup>, for example, having reported outbreaks in 1911 and again in 1948. A similar behavior has held in Massachusetts<sup>20</sup> until recent years when three closely spaced outbreaks occurred in 1942, 1945 and 1948, a matter that calls for interpretation on the basis of altered environmental conditions.

Massachusetts, the rates in epidemic years (1948, 361 per 100,000 population) are essentially twice the average, and some three times those of the usual endemic year. Although absolute values are lower in Illinois, the ratio holds.

The course of the 1948 Massachusetts outbreak illustrates a number of epidemiologic characteristics. The main force of the epidemic was in 1948 and principally in Boston and adjoining industrial centers of popula-

tion. The start in 1947, was in the rural Berkshire district of westernmost Massachusetts and in the south central part of the state (Figure 1). The spread was east and north to the heavily populated cities of the Atlantic coastline, to produce there a well-marked epidemic in 1948 and a practical exhaustion of susceptibles that year. Transmission of infection was slower in rural areas and in suburban districts so that waves were noted frequently in 1949 as well as in 1948. Conforming to the same behavior pattern, mumps did not invade the sparsely populated eastern Cape Cod region until late summer and autumn of 1948, its appearance then being facilitated in all probability by the thousands of summer visitors who enter the area as temporary residents. The main outbreak on Cape Cod was in 1949, a time when mumps was not generally a state problem. The epidemic spared no part of Massachusetts.

The extent to which a mumps epidemic may develop is just as unpredictable as trying to determine the chances of an individual to have a clinical attack. Siegel and Camp<sup>88</sup> describe an institutional outbreak where a newly admitted child spent 24 hours in one cottage and then was transferred to another, to develop parotitis after a second 24 hours. A sharp outbreak of mumps occurred in the first cottage, and no cases in the second during the subsequent incubation. That mumps is highly infectious before parotitis is well known. The outbreak in the first cottage was therefore not unexpected, but the absence of cases where the clinical case occurred is more difficult to understand. The experience of Smith<sup>59a</sup> at Rugby School in England is informative. Outbreaks over the 50 year period 1893 to 1942 ranged in extent from a single case to an epidemic that involved 42% of the school population. Of 42 re-

corded epidemics, 4 were of major significance with attack rates exceeding 10%. Six were within the 5 to 10% range, 7 from 1 to 5%, and 25 had secondary attack rates of less than 1%. The skin test of Enders<sup>28e</sup> is suggested as an epidemiologic tool for forecasting the probable course of events. In 13 epidemics, populations with positive reactions in excess of 50% had attack rates that did not exceed 5%. With less than 50% positive, the attack rates varied from 10 to 40%.

Much has been said about the nature of the agent, the effectiveness of contact, and community dosage as factors in the size of mumps epidemics. The host is not to be forgotten. Peterborough, Ont., a city of 27,000 people, had not had an epidemic<sup>3</sup> of mumps for 17 years. In the 9 months that followed October, 1941, there were 1182 cases, 1 for every 23 residents. The undue accumulation of susceptibles was the answer to the extensive spread of infection, which involved persons from 4 months to 60 years of age.

Mumps is characterized by its wave-like progression through a population, with a seasonal rise each spring and more pronounced cyclic outbreaks every 7 years or thereabouts. A satisfactory explanation of how mumps infection is carried over in a population from one period of seasonal prevalence to another is not to be had. Parotitis in summer is uncommon and often not reported at all, even in sizable communities. Kilham<sup>60c</sup> studied 25 patients with mumps meningo-encephalitis, during the 1948 outbreak in Massachusetts. Eleven of 13 who had no parotitis were seen from mid-May to early September, which suggests that salivary gland enlargement is a less frequent manifestation of mumps in summer than in winter. Johnson and Goodpasture<sup>57c</sup> in the course of 3 years found it difficult to



induce parotitis in monkeys during the summer months. This is in agreement with the rapid decrease in reported cases of parotitis in man as warm weather approaches. Mumps infection without glandular enlargement is difficult to recognize. The hypothesis that central nervous system infections are the mechanism by which the mumps virus is maintained in a population between seasons requires further field and laboratory study.

year of the war. The broader problem has been presented in an earlier review<sup>11b</sup>, but mumps is a first-class illustration of what happened generally.

Since military attack rates from mumps are invariably greater among recruits than seasoned troops a comparison of conditions in the two last wars is best obtained by examining first those troops stationed in continental United States, and secondly those

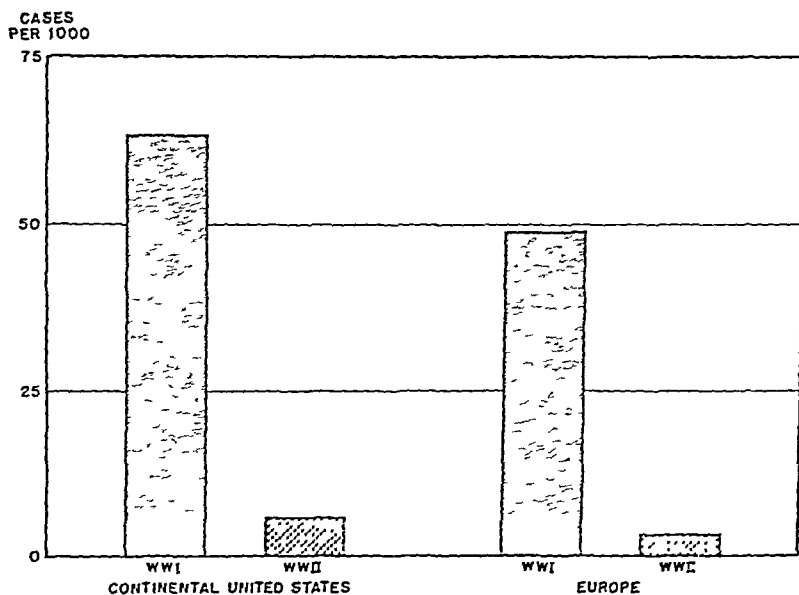


FIG. 2. Mumps, admission rates per 1000 strength, U. S. Army, continental U. S. and European Theater of Operations, World War I (April 1, 1917–Dec. 31, 1919, inclusive) and World War II (Jan. 1, 1942–Dec. 31, 1944, inclusive).

Source: Med. Statist. Div., Off. of The Surgeon General, Dept. of the Army.

*Military.* Most military epidemiologists entered World War II with the conviction that the record for the communicable diseases would be good, and that in all probability the ratio of more deaths from disease than from battle casualties would be reversed, although it had characterized all our previous wars. That almost came about in 1918. What happened was greatly beyond our own personal calculations, although the trend was recognized in the first

in Europe, that being the single foreign theater common to both wars. The data are shown in Figure 2. Admission rates for mumps per 1,000 strength in the United States were 63.4 in 1918 and 5.8 in the second war. The American Expeditionary Force of World War I had an attack rate of 49.1, the European Theater of Operations of World War II a rate of 3.1 per 1,000 strength. Mumps in American troops overseas was one-sixteenth

as frequent in the war just past as it was in 1918; in continental United States the rates were less than a tenth.

The behavior of mumps in Europe in World War II was by no means exceptional, for Table 1 shows much the same situation in all theaters, with the rates in the Pacific and the Far East generally better than in Europe and other more northerly regions.

Mumps in the European Theater of Operations<sup>41c</sup> was a collection of minor events; of isolated outbreaks with no general spread through the command. The common occurrence was for the

and LeHew<sup>23</sup> had responsibility for a small task force where mumps had been endemic for a year, with the number of cases of no particular moment. When the troops went aboard transports the infection flared into an extensive epidemic.

When large numbers of recruits were quickly mobilized<sup>103</sup> respectable epidemics of mumps occurred, as the 1470 cases during a two-year period at Fort Sill<sup>45</sup>, but scarcely matching the outbreaks of the previous war<sup>80</sup>. That the character of the host is a dominant factor in the genesis of epi-

TABLE 1.—MUMPS, ADMISSIONS TO HOSPITALS AND QUARTERS, U. S. ARMY, CONTINENTAL U. S., AND THEATERS OF OPERATION

Cases and Rates per 1,000 Strength per annum by years, January 1942 to December 1945, inclusive.

| <i>Theaters</i>   | <i>Total</i> |             | <i>1942</i>  |             | <i>1943</i>  |             | <i>1944</i>  |             | <i>1945</i>  |             |
|-------------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|--------------|-------------|
|                   | <i>Cases</i> | <i>Rate</i> | <i>Cases</i> | <i>Rate</i> | <i>Cases</i> | <i>Rate</i> | <i>Cases</i> | <i>Rate</i> | <i>Cases</i> | <i>Rate</i> |
| Total Army        | 100,616      | 3.95        | 17,983       | 5.55        | 39,557       | 5.76        | 25,246       | 3.24        | 17,830       | 2.35        |
| United States     | 81,067       | 5.50        | 15,264       | 5.74        | 35,420       | 6.83        | 17,988       | 4.53        | 12,395       | 4.23        |
| North America     | 1,669        | 3.94        | 769          | 7.64        | 797          | 4.10        | 103          | .80         | *            | —           |
| Middle East       | 368          | 3.49        | 4            | .66         | 289          | 5.45        | 75           | 1.62        | *            | —           |
| Europe            | 6,267        | 3.09        | 180          | 2.17        | 941          | 3.53        | 5,146        | 3.07        | *            | —           |
| Latin America     | 752          | 2.44        | 555          | 5.45        | 103          | .85         | 94           | 1.10        | *            | —           |
| Southwest Pacific | 1,344        | 1.68        | 572          | 8.03        | 329          | 1.73        | 443          | .82         | *            | —           |
| North Africa      | 1,734        | 1.53        | 205          | 8.94        | 838          | 1.83        | 691          | 1.06        | *            | —           |
| China-Burma-India | 291          | 1.34        | 32           | 3.66        | 69           | 1.74        | 190          | 1.13        | *            | —           |
| Pacific Ocean     | 978          | 1.11        | 221          | 1.46        | 422          | 1.45        | 335          | .76         | *            | —           |

\* Data not presently available. Source: Dept. of the Army, Office of The Surgeon General, Med. Statist. Div.

disease to appear on board a transport or shortly after troops landed from the Zone of the Interior, with limited outbreaks thereafter in units to which the replacements went. Despite the excellent rates, mumps maintained its position of leadership among the common communicable diseases, to include German measles, measles, meningococcal infection, diphtheria, and scarlet fever. The frequency of mumps was 3 times that of the next most common condition, which was measles.

The crowding aboard transports<sup>71</sup> was a common factor in the spread of mumps in military practice. Dermon

demics of mumps is brought out in the experience of British troops in Cyprus. The island had long been free of mumps, until in 1942 the disease settled solidly in both civilian and military populations<sup>52</sup>, a typical virgin soil epidemic. United Kingdom and Indian troops were largely unaffected. Incidence and complications were high in Cypriots, whether military or civilian.

One of the classical demonstrations of experimental epidemiology is the production of an epidemic in mouse populations by the simple addition of immigrants at regular intervals to an endemically infected colony. The epi-

demic continues as long as new mice are added. What happened with mumps at Fort Benning, Ga.<sup>26</sup>, is the same phenomenon in nature. Mumps started in this training and recruit camp with 250 patients in 1942. The outbreak lasted over the 4 years of the war, with 415 patients in 1943, 955 in 1944 and 836 in 1945. The central focus was the reception center. The outbreak was maintained by continued additions to the personnel of the post.

In this past war the epidemic curve of mumps in military populations differed from that which was usual in World War I, principally in the slower course of the process, in its failure to reach equal heights, and that outbreaks were not so commonly concentrated in the first 2 months of recruit life<sup>79</sup>. The explanation of why mumps was of lesser moment in the war just past appears to lie in altered social and environmental conditions. Increased travel between the two wars presumably led to more general dissemination of the disease and consequently a wider immunity. The experience in Massachusetts of recent years suggests this, that outbreaks are more frequent. McGuinness and Gall<sup>72</sup> at Camp McCoy continued to find a difference in susceptibility between men from the south and southwest and those from other parts of the United States, but Potter and Bronstein<sup>70</sup> state the distinction between rural and urban origin of the soldier is no longer as definite as it was.

**Administrative Control.** A British committee<sup>83</sup> appointed to investigate the periods of incubation and contagiousness of certain infectious diseases reported in 1892 that control based on isolation of patients and quarantine of exposed persons is often ineffective, largely because the infection is highly communicable before the onset of symptoms and the recognition of the disease. Not much can

be added to that, even with all that has been learned about mumps and mumps virus in recent years.

Isolation of patients with mumps is sometimes practiced for unreasonably long periods. Smith<sup>90b</sup> has for many years returned patients to families with susceptible contacts on the eleventh day with no record of a secondary case. Laboratory studies on the persistence of mumps virus in saliva suggest a week as long enough, and common practice of release from isolation when swelling has subsided is certainly safe, and that is about 8 to 10 days.

The benefits to be derived from quarantine of contacts are more in slowing down an epidemic than in limiting the numbers involved; but there is profit in that since medical facilities are not overtaxed, better care is provided and there is the undetermined possibility that virulence in terms of complications is lessened. Interrupted quarantine<sup>43</sup> is presumably as effective as continuous restriction and saves much time. The institution of a working quarantine was still practiced in control of mumps in some military circles during the recent war, although happily not generally. As demonstrated so many times, it proved wholly useless.

The newer methods for limiting airborne and droplet infections have not been widely tried in the control of mumps. Wells, Wells, and Wilder<sup>100</sup> used ultraviolet light irradiation in schools and concluded that less spread occurred in irradiated compared with non-irradiated classes, but the results were not clear cut.

The report of Levine<sup>68</sup> on a sponsored epidemic of mumps should not be missed. Practicing quarantine of immediate contacts and partial quarantine of classes, a private school had been largely free of mumps for 12 years. The next year nature was permitted to take its course, with no

attempt to limit the spread of the infection, in the belief that individuals might do well to build up an early immunity by experiencing the disease in childhood. In the course of 3 months 62 of 114 estimated susceptibles contracted mumps; infection spread to 1 teacher and 10 parents; all of which makes a real epidemic of mumps. The circumstances scarcely provided a fair test. With mumps absent for 12 years, what happened is not unexpected. Observations over a period of years beginning after a natural epidemic might have led to other conclusions than that it was not to be tried again.

The course of mumps epidemics is variable, and attack rates have a wide range. More than the usual care, together with adequate controls, is needed to interpret success or failure in control measures<sup>7,88</sup>. No great promise is provided by any of the available administrative practices. An effective specific prevention offers most in satisfactory control of mumps where that is socially and medically desirable.

**Specific Preventive Measures.** The prospect of improved specific preventive measures is a direct sequence of increased familiarity with the infectious agent. Serums from patients recently convalescent from mumps have been used for many years in passive protection, but with no method of assaying the product or determining its probable worth other than by clinical trial. As a consequence of mumps virus being more readily available, and in quantity, there is now the additional promise of a practical method for active immunization.

*Passive Protection.* Little new evidence has been introduced by which to judge the effectiveness of convalescent serum in the prevention of mumps among susceptible contacts. The position remains none too clear, although experience would indicate better results in mumps than with some other

infections. Wesselhoeft<sup>102</sup> states convalescent serum to have value in preventing an epidemic, but none in limiting an outbreak that is well underway, which is also the experience of Lyday<sup>70</sup>. That results sometimes conflict seems to depend on variations in antibody titer from one lot of serum to another, and on differences in the amounts administered. The first factor is now amenable to measurement, for the content of antibodies can be determined by a variety of serological methods. The greater promise would seem to rest, however, in gamma globulin fractions<sup>10</sup> derived from convalescent serum. Substitution of this product would also eliminate the possibility of outbreaks of serum hepatitis<sup>8</sup> which have followed use of native mumps convalescent serum and plasma.

The well established opinion that convalescent serum is without value in limiting the frequency of orchitis or other complications of mumps when administered at the onset of parotitis, has been further corroborated<sup>5</sup>; and likewise its ineffectiveness in the treatment of fully developed orchitis<sup>81</sup>. Gamma globulin prepared from convalescent serum appears to be another matter. Gellis, McGuinness, and Peters<sup>38</sup> administered this preparation intramuscularly to patients with parotitis of 24 hours or less, in amounts of 20 ml. It was highly effective, in that the frequency of orchitis in treated patients was 7.8% and for controls 27.4%. Gamma globulin prepared from pooled normal plasma and known to possess a high content of complement fixing antibodies for mumps<sup>28c</sup> was without demonstrable effect, even when given in much larger doses than those employed for fractions originating from convalescent serum.

*Active Immunization.* Successful active immunization of monkeys was brought about by Johnson and Goodpasture<sup>57b,57c</sup>, through spraying the

nose and throat with virus-containing materials. The monkey is a relatively resistant host for mumps virus. Latent infection and a solid immunity followed. Attempts actively to immunize man have followed two principal lines: through use of inactivated virus<sup>31</sup>, and through inoculation of modified living virus<sup>33</sup>. The method suggested by Leineberg<sup>64</sup> of intracutaneous injection of defibrinated blood from patients with early mumps scarcely appears practical or safe.

A successful vaccine against mumps would fill a clearly defined need. With mumps the mild infection that it is, a general program of immunization in childhood would likely never be supported, nor indicated. Such a preparation would find a place in the practice of preventive medicine as contrasted with public health, through selective use for children with other disease or living in situations where an attack of mumps would prejudice the general health. It would have a place in institutions for children, where a protected environment often leads to long absence of infection and the groundwork for sharp epidemics. An essential feature of such a vaccine would be a long enduring immunity or a protection readily reinforced; otherwise, mumps would merely be postponed to a later and more dangerous age. The principal usefulness of a good mumps vaccine would be in military practice or under similar situations where large numbers of young adults are quickly brought together. The ability to sort out susceptibles by skin test gives active immunization an added practicability.

The first prophylactic mumps vaccine<sup>31</sup> was made with formaldehyde-treated virus from the parotids of infected monkeys. Introduced into normal monkeys, the preparation produced no local swelling of the salivary glands, but did give rise to comple-

ment fixing antibodies, with a maximum titer on the eighteenth to thirtieth day. Some 60% of vaccinated animals had a slight but distinct resistance to subsequent infection with viable mumps virus. Evidence of increased resistance and the presence of complement fixing antibody did not always parallel each other. Clinical tests in human beings<sup>92</sup> showed the same slight but ineffective immunization after repeated subcutaneous injections of the formaldehyde-treated virus.

With the successful cultivation of mumps virus in the hen egg, Habel<sup>44c</sup> prepared a vaccine by inactivating egg material through exposure to ether or to ultraviolet irradiation. Monkeys were successfully immunized as judged by absence of parotid swelling after test inoculation and by antibody response. The results of Beveridge and Lind<sup>9b</sup> were less impressive.

Enders and his associates<sup>33</sup> have had encouraging results with a viable mumps vaccine. After 25 serial passages in the embryonated egg, mumps virus lost its capacity to induce typical experimental parotitis in the monkey, when introduced by Stenson's duct, but nevertheless retained its ability to immunize. Tested 6 to 14 weeks later, the vaccinated animal exhibited a solid resistance. Furthermore, the modified virus was no longer pathogenic for man when applied by spraying to buccal mucous membranes. Particular attraction attaches to the possibility of an immunization brought about by so simple a procedure as spraying material into the mouth. That would be a welcome respite from the world of needles that a child, and his parents, now face. Field trials to determine the immunizing capacity of these new preparations are now underway.

The results that Habel has had with his inactivated egg virus vaccine<sup>44c</sup> are presented here in advance of formal

publication and by his permission<sup>44d</sup>. Immunization was generally through a single subcutaneous injection of vaccine, although some few persons received a second dose. The efficiency of the procedure was measured by the response of vaccinated individuals in antibodies against the mumps virus; and by the protection afforded groups of exposed vaccinated persons. As high or higher titers of neutralizing antibodies followed vaccination as after naturally acquired infection. In test

groups numbering several thousand persons the frequency of mumps among controls was 3 times that among the vaccinated. The mumps that occurred within 3 weeks after vaccination was of normal severity, but thereafter was much modified as judged by clinical reaction, and frequency of complications. There was reason to believe that if a sufficient proportion of a population was vaccinated in the course of an epidemic, the outbreak was effectively limited.

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# BOOK REVIEWS AND NOTICES

**THE EPIDEMIOLOGY OF HEMOLYTIC STREPTOCOCCUS.** By ALVIN F. COBURN, M.D., and DONALD C. YOUNG, M.D., The Rheumatic Fever Research Inst., Northwestern Univ. Pp. 229; 31 ills. Balt.: Williams & Wilkins, 1949. Price, \$4.00.

This is a well-written and graphically illustrated book. There are 21 chapters, each with its own summary, and the 22nd chapter which is a summary of the previous chapters. The Authors state that this book is a "report from 'the field'". It makes no contributions to the fundamental knowledge of bacterial life or of human disease; nevertheless, it does make facts available which no other period of American history has afforded." The various points discussed in the book are too numerous to list in a review. The reader will find frequent mention of the Author's theory of communicability as one of the attributes of hemolytic streptococci. Epidemiologists, public health workers, bacteriologists, and others interested in streptococci or airborne infection will find this book interesting and supplying much food for thought. H. M.

**SKELETAL TUBERCULOSIS.** By VICENTE SANCHIS-OLMOS, M.D. Translated from the Spanish by JOHN G. KUHN, M.D. Foreword by FRANK R. OBER, M.D. Pp. 261; 104 ills. Balt.: Williams & Wilkins, 1948. Price, \$5.00.

This book is based largely on the author's extensive experience in his native Spain, as well as on case reports gathered during his stay in the United States. Emphasis is placed on the new or little known, rather than exhaustive completeness. Nevertheless, all important aspects of skeletal tuberculosis are presented, in a thesis well knit by convincing doctrinal concepts. The book appears to suffer not at all in translation.

The first section, approximately half the book, is a general discussion that covers pathology, etiology, symptomatology, diagnosis and treatment. The remainder is concerned with tuberculosis of special regions of the skeleton, such as the skull, ribs and sternum, knee joint and elbow joint. There are many good illustrations, most of them roentgenograms, a few charts and photographs. A bibliography of several hundred references, approximately a third of them in English, is appended. C. B.

(360)

## NEW BOOKS

*Die Ermittlung des Erregungsablaufs in ungeschädigten und durch Analyse des und des Vektordiagramms.* VON LOTHAR WENDT. Pp. 84; 29 ills. Berlin: Akademie-Verlag, 1949. Price, 12.50 D.M.

*Conference on Metabolic Aspects of Convalescence.* Edited by EDWARD C. REIFENSTEIN, JR., M.D. Trans. of 16th and 17th Meetings, October, 1947, March, 1948. Pp. 168 and 246. Illustrated. New York: Josiah Macy, Jr. Foundation. Price, \$3.00 and \$4.00, respectively.

*Problems of Early Infancy.* Edited by MILTON J. E. SENN, M.D. Transactions of the 2nd Conference, March, 1948. Pp. 120. Illustrated. New York: Josiah Macy, Jr. Foundation. Price, \$1.00.

## NEW EDITIONS

*A Dictionary of Scientific Terms.* By I. F. HENDERSON, and W. D. HENDERSON. Revised by JOHN H. KENNETH, M.A., Ph.D., F.R.S.E. 4th ed. Pp. 480. Edinburgh and London: Oliver and Boyd, 1949. Price, 32 s (\$6.40).

THOUGH 2000 terms have been added in this edition, the desire to maintain an "acceptable format and typography" has blocked plans for a considerable expansion. However, with the wide range of subjects this in any case would have been inadequate. To the Reviewer it would have been wiser to have eliminated items of human anatomy, embryology, and so on, which are more fully covered in several excellent medical dictionaries, and thus permit a more adequate treatment of botanical and zoological terms. E. K.

*Cardiovascular Disease in General Practice.* By TERENCE EAST, M.A., D.M., F.R.C.P., King's College Hospital, London. 3d ed. Pp. 208; 34 ills. Phila.: Blakiston, 1949. Price, \$4.00.

"THERE is a good deal of new material in the sections on heart failure, and its treatment; and on coronary occlusion, hypertension, thyrotoxicosis, congenital defects, pulmonary disorders, and peripheral failure." (From Preface)

*The Complete Pediatrician.* By W. C. DAVISON, Prof. of Pediatrics. 6th ed. Pp. 256. Durham, N. C.: Duke University Press, 1949. Price, \$4.75.

This compendium of useful information is again brought up to date. It is deservedly popular as a ready reference for the thousands of facts essential to the thorough practice of pediatrics. I. W.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### A STUDY OF FACTORS AFFECTING THE PROGNOSIS OF CEREBRAL VASCULAR ACCIDENT

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EXCEPT for a study by Brown<sup>2</sup>, the problems pertinent to prognosis in cerebral vascular accidents have received only incidental attention. Although several authors<sup>5,6,7,9,12,14</sup> suggest factors which seem to influence the prognosis and a few of them discuss longevity in cerebral vascular accidents, none attempts to establish prognostic criteria. Such criteria, as vicarious adjuncts to the necessary clinical experience, appear to be needed urgently, especially as cerebral vascular accident is one of the commoner causes of death and incapacity. In view of this, it was decided to study the pattern of behavior manifested by a series of spontaneous acute cerebral vascular accidents, in order to appraise the formulation of prognostic standards.

**Material Studied.** The cases studied were all admissions to the Wisconsin General Hospital. All syndromes due directly to trauma, infection, neoplasia, hemorrhagic blood dyscrasias and congenital anomalies were excluded, leaving only the acute spontaneous

cerebral vascular accidents. The diagnoses were carefully re-analysed in accordance with the work of Aring and Merritt<sup>1</sup> to segregate them into their groups of hemorrhage thrombosis and embolism.

In Table 1 are enumerated the criteria, derived by Aring and Merritt

TABLE 1.—CRITERIA FOR THE DIFFERENTIAL DIAGNOSIS OF CEREBRAL VASCULAR ACCIDENT

| Sign                            | Hemor-<br>rhage | Throm-<br>bosis | Embolism |
|---------------------------------|-----------------|-----------------|----------|
| Syncope                         | +++             | +               | ±        |
| Cephalalgia,<br>severe, sudden  | +++             | +               | ±        |
| Emesis                          | +++             | ++              | +        |
| Convulsions                     | ++              | +               | +        |
| Coma                            | ++              | ±               | +        |
| Bloody spinal<br>fluid          | +++             | ±               | ±        |
| Raised spinal<br>fluid pressure | +++             | ±               | ±        |
| Nuchal rigidity                 | ++              | +               | ±        |
| Signs progressive               | ++              | ±               | ±        |
| Embolic disease                 | ±               | ±               | +++      |

+++ = Usual

++ = Frequent

+ = Infrequent

± = Rare

from a clinico-pathologic study of 245 fatal cases of cerebral vascular accident, as we employ them to establish our differential diagnoses. Notwithstanding the usual clearcut differences, the distinction of the types is not always simple. There is no one clinical sign by itself which can decide the differential diagnosis. The types may so closely approximate one another and overlap that they are occasionally indistinguishable. In making a diagnosis, Aring and Merritt, and later Levy<sup>8</sup>, stress the necessity of a careful analysis of the history, together with the results of the physical and neurological examinations and of the examination of the cerebrospinal fluid. They indicate that on this basis differentiation is possible in nearly 100% of cases. Of the 26 cases dying in our institution, autopsy permission including examination of the brain was obtained in 12. The autopsy substantiates our diagnosis in 11 of these (92%). We assume, therefore, that the criteria of these investigators, as we use them, obviate the diagnostic difficulties in the majority of our cases.

On the basis of a rigid selection, 107 cases are finally accepted as examples of primary acute cerebral vascular accident, with data adequate to our purposes. The significant information concerning age, sex, variation in blood pressure, abnormality of respiration and cerebrospinal fluid analysis is obtained from the protocols of each case. Insofar as the blood pressure is difficult to evaluate immediately subsequent to a cerebral accident, it was decided to use the highest pressure recorded during hospitalization, as has been done by other investigators. On the contrary, no attempt is made to localize the exact site of the cerebral lesion, because in acute cases such as ours the lability of neurological signs stultifies the value of anatomical localization<sup>15</sup>. In such cases as survived

the initial attack, an attempt has been made to determine the occurrence of subsequent accidents, the longevity and the patient's state of health at the time of inquiry. This investigation reveals the subsequent histories of 65.4% of those who survived the first cerebral vascular accident, with details sufficient for our analysis.

Among the 107 selected cases of cerebral vascular accidents there are 75 cases of hemorrhage, 27 of thrombosis, and 5 of embolism, with an aggregate of 132 separate attacks. Fourteen patients (13%) have suffered more than one attack, ranging from 1 to 5 episodes. There are 26 fatalities on the initial attack, with 81 survivors, of whom 53 are traced adequately. Among those whom we traced, 33 are known to be alive at the time of the study. The relative proportions of hemorrhage, thrombosis and embolism in our series are similar to those of Aring and Merritt<sup>1</sup>, although we believe that neither their nor our figures represent the true general incidence. In Courville's<sup>4</sup> series of 15,000 autopsies, there were 569 cases of cerebral thrombosis and 388 cases of cerebral hemorrhage; when these are so analysed as to exclude cases which are not primary, the ratio is still 497 to 208 in favor of thrombosis. An almost simultaneous clinical survey of 600 cases by Merritt<sup>10</sup> illustrated an incidence of 66% for thrombosis and 21% for hemorrhage. Some authors believe that the preponderance of hemorrhage in their autopsy series is because most cases of thrombosis recover to a sufficient extent to leave hospital. It is our experience, perhaps due to certain geographical peculiarities, that because they are milder, the thromboses are not sent to our institution, whereas the severer cases of hemorrhage are. Because of this our examples are weighted by the number of hemorrhages.

**Results of Analysis. Age.** The majority of cases in the present series occurred between the fourth and seventh decades, with the highest incidence in the sixth. The mean average is 56 years and approximates expectation. There are relatively few cases before 40 years of age; only 12 of our cases fall into the younger categories, with 10 of these in the fourth decade. The type of accident is not peculiar to any age. Our examples of embolism, however, are too few to permit inference concerning them and, because we have not included cases of cerebral vascular accident secondary to other

increases as that group deviates from the age group of highest incidence. Such cerebral vascular accidents as occur prior to 40 and later than 60

TABLE 2.—THE AGE INCIDENCE OF CEREBRAL HEMORRHAGE AND THE PERCENT MORTALITY ACCORDING TO AGE IN 75 CASES

| Age Group (years) | Number of Cases | Percent Incidence | Number Fatal | Percent Fatal |
|-------------------|-----------------|-------------------|--------------|---------------|
| 10-29             | 2               | 2.6               | 1            | 50.0          |
| 30-39             | 8               | 10.6              | 3            | 37.5          |
| 40-49             | 10              | 13.4              | 3            | 30.0          |
| 50-59             | 26              | 34.6              | 5            | 19.2          |
| 60-69             | 19              | 25.4              | 5            | 26.3          |
| 70-79             | 10              | 13.4              | 5            | 50.0          |
| Total             | 75              | 100.0             | 22           | 29.2          |



FIG. 1.—The divergence of incidence and mortality rate of cerebral hemorrhage with increasing age up to the age of 50 is demonstrable. The approximation of these is seen at the extremities of life.

disease, our representation of embolism may not correspond to the true incidence.

When the instances of cerebral hemorrhage are separated into fatalities and survivals, it emerges that, whereas the number of fatalities rises slightly with age, it is far less than proportionate to the increased incidence of such accidents (Fig. 1). The disparity between incidence and mortality percentage is most extreme at the age of greatest occurrence. It is furthermore apparent (Table 2) that the percentage mortality per age group

years are more likely to be fatal than an attack occurring between these ages. That this applies to accidents in children is open to question, since but 2 of our cases were under 30 years of age.

The cases of thrombosis in the present series have a similar age distribution to those with hemorrhage. But the mortality rate on first attack is so low, 2 instances among 27 thromboses (7.5%) that the condition is a striking contrast to hemorrhage, in which the mortality was 29.2% in the first episode. It is deduced from this

that age is not so clearly a factor in deaths from cerebral thrombosis as it is in hemorrhage. Age, which assumes considerable importance in the latter type of accident, is of relatively slight significance in the thrombotic accidents; wherefore the accurate delimitation of these two types is of the utmost value.

**Blood Pressure.** The cases of cerebral hemorrhage after the initial attack are divided into fatalities and recoveries, and their blood pressure readings, both systolic and diastolic, are compared. It becomes apparent that until the systolic pressure is elevated above 190 mm. Hg., and the diastolic rises beyond 140, the mortality percentage is not appreciably affected in relation to blood pressure. With pressures above these readings a significant augmentation of mortality ensues (Tables 3 and 4), when

TABLE 3.—RELATIONSHIP OF MORTALITY PERCENTAGE AND SYSTOLIC BLOOD PRESSURE IN FIRST ATTACK OF CEREBRAL HEMORRHAGE

| Systolic Pressure (mm. Hg.) | Number of Cases | Number Fatal | Percent Fatal |
|-----------------------------|-----------------|--------------|---------------|
| 100-139                     | 20              | 3            | 15.0          |
| 140-169                     | 19              | 4            | 21.0          |
| 170-189                     | 12              | 2            | 16.0          |
| 190-260                     | 24              | 13           | 54.1          |
| Total                       | 75              | 22           | 29.2          |

TABLE 4.—RELATIONSHIP OF MORTALITY PERCENTAGE AND DIASTOLIC PRESSURE IN 75 CASES OF FIRST ATTACK OF CEREBRAL HEMORRHAGE

| Diastolic Pressure (mm. Hg.) | Number of Cases | Number Fatal | Percent Fatal |
|------------------------------|-----------------|--------------|---------------|
| 60-99                        | 31              | 8            | 25.8          |
| 100-139                      | 35              | 8            | 22.8          |
| 140-190                      | 9               | 6            | 66.0          |
| Total                        | 75              | 22           | 29.2          |

such pressures are found subsequent to the accident. Which reading, systolic or diastolic, is of greater value is still problematic, but from the present series it appears that, as an indicator, the systolic has a slight advantage as compared with the diastolic pressure.

The average blood pressure of the fatal cases is 197/115, and 75% of them have pressures above normal. It is pertinent that, among the fatal cases with normal pressures, 4 were affected by severe complicating diseases which significantly contributed to the mortality. With the exclusion of these cases the remainder have an average systolic pressure of 211 mm. Hg. and a diastolic of 122. On the other hand, the average pressures for the recovered cases are 168 mm. Hg. systolic and 102 diastolic. By treating the groups comparably and eliminating cases with severe complications, these distinctly lower pressures are not altered. Although the number of deaths by thrombosis following the first attack is too small for significant subdivision, it is noteworthy that the pressures in the 2 fatal instances have been normal. On the other hand, the mean average pressures for the entire group of thromboses are 174 mm. Hg. systolic and 105 diastolic, which figures approximate those found for the recovered cases of cerebral hemorrhage.

Superficially it would appear that considerable significance might be attached to these figures and that very high blood pressure may be a decisive factor. However, when statistically analysed by the method of Chi squares, the element of chance variation cannot be excluded rigidly. The deviation from the required result after the statistical treatment is small enough, nevertheless, to indicate that a more extended series may substantiate the suggested significance of the difference in pressures between the fatal and non-fatal groups.

**Recurrence of Attacks.** Consideration of the repetition of attacks in cerebral vascular accident entails 2 problems. One is that of the expected mortality in each succeeding episode, and the other concerns the probability of a subsequent attack. In cerebral hemor-

rhage (Table 5) the mortality after a first attack is 29.2%, after a second 30%, whereas succeeding third and fourth attacks have a 50% and 100% mortality respectively. The examples of third and fourth attacks are so few that these figures are not significant. But there is no difference between the mortality rates of first and second attacks. It is of further interest that the combined mortalities of the attacks other than the first represent 11% of all those patients surviving the first attack. Since the mortality of first and second attacks of hemorrhage is similar, the probability of a repetition gains added interest. Ten (18.8%) of the survivors of the initial cerebral hemorrhage developed one or more acute attacks. With this low probability of a succeeding event and the same mortality for

tacks of cerebral hemorrhage is 46 months with a wide range of variation. In fatal cases of second episode the interval measures 12 months, whereas in non-fatal second attacks the interval is 76 months. This discrepancy is further substantiated by the fact that the average duration between second and third attacks is 2 months for the fatal and 10½ months for survivors. This may indicate that the mortality is inversely proportional to the length of time between attacks of hemorrhage; the sooner the recurrent attack ensues the more likely it is to be fatal. However, this is merely an indication which requires the confirmation of a larger series of cases.

*Coma and Respirations.* Two additional phenomena are found to bear upon prognosis; these are coma and

TABLE 5.—THE RELATIONSHIP OF RECURRENT ATTACK AND PERCENTAGE OF MORTALITY IN 75 CASES OF CEREBRAL HEMORRHAGE, 27 OF THROMBOSIS AND 5 OF EMBOLISM

| Attack | Hemorrhages |              |               | Thromboses |              |               | Embolisms |              |               |
|--------|-------------|--------------|---------------|------------|--------------|---------------|-----------|--------------|---------------|
|        | Cases       | Number Fatal | Percent Fatal | Cases      | Number Fatal | Percent Fatal | Cases     | Number Fatal | Percent Fatal |
| 1st    | 75          | 22           | 29.2          | 27         | 2            | 7.5           | 5         | 2            | 40            |
| 2nd    | 10          | 3            | 30.0          | 2          | 1            | 50            | 2         | 1            | 50            |
| 3rd    | 4           | 2            | 50.0          | 1          | 0            | 0             | 1         | 0            | 0             |
| 4th    | 1           | 1            | 100.0         | 1          | 1            | 100           | 1         | 0            | 100           |

such an occurrence, the hazard from this direction may be regarded as appreciable but not major. Since the incidence of the second attack is 18.8% and the mortality of such an episode is 30%, it may be deduced that the expectation of any survivor that he may die of such an occurrence is 5.6% or approximately 1 in 20. For cerebral thrombosis the mortality after the initial attack is very low (7.5%) and subsequent attacks in our series are too infrequent to allow further analysis, although this rarity of recurrence appears contrary to clinical experience in thrombosis.

*Duration between Attacks.* The average time between first and second at-

abnormal respiration. Whereas the depth of coma is unrelated to the outcome of the cerebral vascular accident, the duration is of considerable importance. In the 22 fatal cerebral hemorrhages, the duration is several hours, and in 4 instances is stretched beyond 2 days. In the cases which recovered, such coma as was observed lasted no longer than 2 hours in any instance. On the other hand, all except 6 of the fatal cases (76.9%) have exhibited prolonged periods of abnormal respiration, particularly the Cheyne-Stokes phenomenon. The cases which recovered have manifested only transient episodes of abnormal respiration. In the fatal cases which have lacked res-

piratory abnormality, the period of survival time is 11.6 days, compared with 7.9 for the remainder who have manifested severe symptoms. Prolonged coma and protracted episodes of abnormal respiration may be said to emphasize the gravity of immediate prognosis.

**Discussion.** In his assessment of cases of cerebral vascular accident, the clinician is confronted with two problems of prognosis. One is the immediate prognosis of any case in its acute phase, an exceedingly difficult task; the other is the ultimate or "long term" prognosis, which is the outlook in such cases as recover from an attack. The immediate prognosis will in a large measure depend upon the type of accident; there is a 30% mortality in hemorrhage compared with a 7.5% mortality in thrombosis, whereas in cerebral embolism the future is colored by the associated disease responsible for the emboli. It is most important, therefore, to separate the conditions by an accurate diagnosis, since it so substantially affects the prognosis.

Among the features which may so characterize a cerebral vascular accident as to sway the prognosis, are the age of the patient, the duration of coma, the presence of atypical respiration and the height of the blood pressure. In our series there is strong evidence that the mortality varies with age, and that it is greatest at the extremes of life, least during the fifth and sixth decades. This would indicate that during these decades the prognosis is more favorable. Of the cases in our series which sustained coma and recovered, the duration did not exceed 2 hours. MacDonald<sup>9</sup> avers that coma lasting for longer than 48 hours is a very bad sign; to this our experience attests. Moreover, although brevity and absence of coma may not preclude a fatal outcome, they indicate a more favorable prognosis. On the other hand,

the occurrence of atypical respiration, particularly if prolonged or of Cheyne-Stokes variety, is a sign of considerable gravity. All except 6 of our fatalities manifested this sign. Aring and Merritt<sup>1</sup> mention that Cheyne-Stokes and other forms of respiration are frequent in their series and that a practically constant finding in any type of accident is the uniform rise of temperature, pulse rate and respiratory rate several hours or days before death. With this our studies agree.

With regard to blood pressure, we tentatively regard a very high pressure as unfavorable. Although exact figures have limited value, a systolic pressure over 190 mm. Hg. and a diastolic over 140 suggest a poor prognosis. As was shown above, the statistical analysis fails to satisfy the requirements for complete exclusion of chance variation, but suggests a more extensive study. The height of the pressure may serve, therefore, as an indicative though not conclusive sign. Its value is enhanced by the behavior of the pressure in thrombosis, where it has been so low as to approximate that of non-fatal cases of hemorrhage, and where it is also associated with a very small mortality. Since we did not use blood pressure as a criterion for our selection of thrombosis, we regard this correlation as significant. It is pertinent from the investigations of Rasmussen and Bøe<sup>13</sup> that the mortality due to cerebral vascular accident in cases of essential hypertension bears a distinct relation to the height of both systolic and diastolic blood pressures. They further emphasize the great prognostic significance of the height of blood pressure. The relationship drawn by them closely approximates our findings; in both studies not only is a rising mortality demonstrated with an increasing pressure, but the levels of systolic and diastolic pressures, at which the increased mortality is clearly manifest,

are similar. Although the purposes of the studies in these instances are quite different, a similar conclusion is reached, namely that the height of blood pressure significantly affects the prognosis of cerebral vascular accidents. The discrepancy in our series between the systolic and diastolic blood pressures as a factor affecting the outcome of these cases further suggests that the intermittent distending force of an elevated systolic pressure plays a greater role than the continuous stress due to the maintained diastolic level. With our thinking oriented by the cardiological concept of the major importance of the diastolic pressure, against which the heart labors, we have perhaps lost sight to some extent of the fact that the peripheral vasculature may be very severely taxed by the force of the systolic pressure wave. Courville indicates that, regardless of the nature of the predisposing focal lesion, gross cerebral hemorrhage is the result of rupture of an artery no longer able to withstand the intravascular pressure incident to cardiac systole. It is probable, therefore, that the difference in the relationship of systolic and diastolic pressures to mortality is due to their dissimilar effects upon the peripheral vasculature.

The ultimate prognosis of a case depends not so much upon the features peculiar to the case as upon our understanding of average expectations. Longevity, so far as the disease itself is concerned, will be determined by the recurrence of attacks and the mortality characteristic of the recurrences. Brown<sup>2</sup> carefully followed a series of 120 cerebral vascular hemorrhages with a mortality of 35% on the first attack, which corresponds well with our 29.3%. This author indicates a rising mortality with subsequent attacks, whereas we found the same incidence in our first and second attacks of hemorrhage, 29.3% and 30% respectively,

and could regard neither Brown's nor our own figures of third and fourth attacks as adequate for analysis. We cannot, therefore, fully agree that "the mortality in cerebral hemorrhage is directly proportional to the number of strokes the patient has had," especially since the rate of recurrence is low and the mortality does not vary. In our series, 18.8% proceeded to a second attack, so that the chances of death on a recurrence are approximately 1 in 5. If maximal overcompensation could be made for the unfollowed cases, the figure would rise to 34%, which is close to Brown's figure of 40% with second attacks. But more important is the fact that from both Brown's and our studies it may be concluded that the liability of death by a subsequent attack is less than half the rate encountered in the initial attack, or between 11% and 20%. Mortality in the second attack represents only 5.6% of the survivors.

With this estimation of the incidence of repeated attacks and mortality therefrom, the ultimate prognosis may be considerably narrowed. The expectation of life may be parallel to that of the person's age group, unless a recurrence and sequelae are such as to compromise vital functions, which is in part decided by the location and extent of lesions. Gintrac<sup>6</sup> in 1869 was perhaps the first to report on this phase of the problem when he stated that of 667 cases of hemorrhage, 106 lived to between 4 and 10 years, and 8 patients survived over 10 years. It was later observed by Charcot<sup>3</sup> that in an institution for the infirm, of 1,000 invalids, 200 were hemiplegics for some duration. In a commentary<sup>11</sup> upon the difference between the numbers of cases of cerebral vascular accident clinically controlled and those analysed by autopsy, of which there were 604 and 245 respectively, it is pointed out that these two contrasting groups empha-



size the fact that cerebral vascular accident does not always carry with it a fatal outcome. It is further indicated that many patients may survive 10 years and even longer. In our small series, 3 have survived for over 10 years, one of these for 25 years, 6 other patients are alive after 5 years and the remainder for variable shorter times. Brown mentions a case surviving for 18 years. A considerable survival is possible, though very long intervals are uncommon. However, since the extent of the damage, its location and the age of incidence are most probably very important factors in longevity, an exact appraisal can come only from an extensive accumulation of such data. Since the majority of these accidents occur in the geriatric period of life, their longevity may be most accurately assessed by close comparison with their contemporary collaterals. By this it is feasible to determine how short they fall of their life expectancy and whether the demise is directly attributable to the cerebral vascular accident. Our indications suggest that these

patients have a good chance of living out their expected life span once they survive the initial attack and suffer no recurrences.

**Summary and Conclusions.** 1. The correlation of clinical data concerning age, sex, blood pressure and physical signs has been made on 75 cases of cerebral hemorrhage, 27 of thrombosis and 5 of embolism. Of these, 64.5% were followed up successfully.

2. In the assessment of immediate prognosis, age, the duration of coma, type of respiration, and an elevation of blood pressure offered valuable assistance. The type of accident is also important, since 30% of hemorrhages and 7.5% of thromboses are fatal in the first attack.

3. Of the survivors of hemorrhage about 18% have one or more recurrences; 5.6% of these die in the second attack and 11% of the combined subsequent attacks. Unless seriously compromised by the sequelae of the disease, the remaining survivors seem to live out their expected life span.

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# MAJOR ETIOLOGICAL FACTORS PRODUCING DELAYED RESOLUTION IN PNEUMONIA\*

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THE patient with pneumococcal pneumonia, treated with penicillin or the sulfonamides, generally responds with dramatic clinical improvement within a few days, and shows complete resolution manifested by disappearance of physical and roentgenological signs within a period of 2 to 4 weeks. Cases frequently occur, however, in which this uneventful and desirable course does not ensue. In an attempt to determine the factors responsible for delayed resolution, a study has been made of 198 cases of pneumonia admitted to this hospital during its first 2 years of operation. The hospital has been designated as a chest center for the Veterans Administration, and 47 of the above patients who were received had been treated for pneumonia prior to admission. Of these 198 cases, 52 (26.2%) exhibited delayed resolution.

Delayed resolution or unresolved pneumonia includes a number of different pathological conditions. It is a useful clinical term and not an expression of a specific pathological entity. It must be emphasized that the term should not be employed without being qualified by a pathological or bacteri-

ological explanation. In selecting cases for this series, an arbitrary time limit for complete resolution was set at 30 days.

It is rather surprising to note the paucity of published reports on this subject. A review of the British and American literature during the last 20 years reveals only three articles pertaining specifically to the etiology of unresolved pneumonia<sup>1,4,5</sup>. This is almost certainly due to the fact that many of the so-called unresolved pneumonias, on reaching the pathologist, are correctly classified as to their proper etiology: for example, malignancy, lung abscess, bronchiectasis, lipoid pneumonia, and others. Although many of the cases of delayed resolution have their origin in underlying disease, instances occur in which no obvious basis can be detected for the delay in proceeding to complete resolution. These must fall in the group of chronic pneumonias. The etiological factors responsible for this delay may not be readily apparent, but on more thorough and detailed study can be demonstrated in almost every instance. Pickhardt<sup>4</sup>, in 1928, studied 46 patients with chest

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conditions in whom a diagnosis of unresolved pneumonia had been made, and he was able to determine the specific disease process present in all but 6 cases. Of this series, 37.5% proved to be surgical conditions.

The consideration of etiology must involve a discussion of 3 groups of factors. The first of these is the group of bacteriological and chemical factors (Table 1). *Klebsiella pneumoniae*,

TABLE 1. BACTERIOLOGICAL AND CHEMICAL FACTORS IN DELAYED RESOLUTION

1. *Klebsiella pneumoniae* (Friedlander's Bacillus)
2. *Diplococcus pneumoniae*--Type III
3. *Streptococcus*
4. *Staphylococcus*
5. *Pasteurella tularensis*
6. *Mycobacterium tuberculosis*
7. Anerobic organisms of the oropharynx
8. Viruses: a. Primary atypical pneumonia  
b. Ormithosis
9. Fungi
10. Aspiration of food or gastric contents
11. Oil aspiration
12. Septic embolism

*Diplococcus pneumoniae*--type III, *Streptococcus*, and *Staphylococcus* are organisms known for their tendency to produce severe and protracted pneumonias in which suppuration and abscess formation often occur. The *Streptococcus* and *Staphylococcus* also possess a strong tendency to produce pleural effusion and empyema. If tularemic infections are not recognized and promptly treated with streptomycin, their course is prolonged. It is rather a common occurrence for a tuberculous pneumonia to go unrecognized in its early stages. The spirochetes and other anerobic organisms of the oropharynx frequently are aspirated during anesthesia, diabetic coma, alcoholic stupors and other forms of unconsciousness. This is particularly likely to occur in individuals with pyorrhea alveolaris. The resulting pneumonias are slow to resolve because of

the necrotizing nature of the infection. Aspiration of food and secretions from the dilated esophagus of the patient with cardiospasm occurs not uncommonly and produces a relatively benign organizing pneumonia, as contrasted with the extensive suppuration and destruction seen with aspiration of gastric contents. Many patients with primary atypical pneumonia show pulmonary infiltration over prolonged periods of time. Chronic fungus infections of the lungs are being recognized with increasing frequency. Aspiration of oil produces a chronic organizing process. Septic embolism should be suspected in protracted migratory pneumonias of lobular distribution in which a single organism is repeatedly isolated from the sputum<sup>1</sup>. There is usually an obvious source of infection elsewhere in the body. The importance of obtaining an early and accurate bacteriological study is much greater now than in the era before antibiotics, since it is mandatory to employ the available specific drugs against the invading organism.

The second major group of processes responsible for delayed resolution includes all the factors which impair bronchial drainage. This includes any condition which obstructs the upper or lower respiratory tract, interferes with normal ciliary action within the bronchus, or impairs the normal mobility and elasticity of the lung parenchyma.

A classification of the factors producing impaired bronchial drainage is given in Table 2. The important endobronchial causes are carcinoma in the older age group and foreign bodies in infants and children. It cannot be emphasized too strongly that, in a patient over the age of 40 with a protracted pneumonia or a history of recurrent attacks of pneumonia involving the same lobe, carcinoma must be seriously considered. This is especially true if a history of blood-streaked sputum or unilateral wheeze is obtained. If bron-

TABLE 2. FACTORS INFLUENCING BRONCHIAL DRAINAGE LEADING TO DELAYED RESOLUTION

1. Upper respiratory obstruction:
  - A. Vocal cord paralysis
  - B. Pharyngeal paralysis
2. Bronchial obstruction:
  - A. Endobronchial disease
    1. Tumor: a. Carcinoma  
b. Adenoma
    2. Foreign Body
    3. Inflammatory disease:
      - a. Tuberculosis
      - b. Non-specific stenosis
  - B. Extrabronchial disease
    1. Aneurysm
    2. Mediastinal tumor
    3. Hilar node enlargement
3. Impaired ciliary action:
  - A. Chronic bronchitis
  - B. Bronchiectasis
  - C. Bronchial asthma
  - D. Arrested pulmonary tuberculosis
4. Impaired pulmonary mobility:
  - A. Pulmonary fibrosis and emphysema
  - B. Pneumoconiosis
  - C. Chest trauma
  - D. Paralysis of diaphragm or intercostal muscles.

choscopy does not reveal the neoplasm, examination of the bronchial washings and sputum for tumor cells by the Papanicolaou technique may yield the diagnosis. However, the failure to obtain positive evidence of the presence of carcinoma by these methods should in no way delay exploratory thoracotomy. This approach has recently been emphasized by Ochsner and his associates<sup>3</sup>. Extrabronchial masses may occasionally compress the lumen of a bronchus, thereby producing inadequate drainage and secondary pneumonia.

Impaired ciliary action resulting in poor drainage of the lung, puddling of secretions, and pulmonary infections which are slow in clearing are seen in patients with bronchitis, bronchiectasis and asthma. This process may also occur in lobes which were once the site of a tuberculous process. Fibrosis, emphysema and inadequate blood supply with impaired aeration of the re-

gion undoubtedly play an important role.

There is little doubt that the ventilation and drainage of the peripheral lung tissue are greatly impaired in conditions in which pulmonary mobility is lessened. The fibrotic and emphysematous lung has little elasticity, and the force of the expiratory air blast, which helps expel secretions from the alveoli and bronchioles, is impaired. The peristaltic action of the bronchioles is also diminished, adding further to the inadequate cleansing of the affected broncho-pulmonary segment. The same mechanism is present in patients whose pneumonia is associated with chest trauma. Here the lung is splinted by fractured ribs and pleurisy, and bronchospasm and interstitial hemorrhage are prominent features. If adequate amounts of an analgesic drug are administered, or, better yet, if regional nerve blocks are performed to relieve the pain, the effects of trauma may be minimized. Finally, it is apparent that poliomyelitis and other neurological diseases which produce paralysis of the diaphragm, the intercostal, the laryngeal, or the pharyngeal musculature may cause delayed resolution by interference with bronchial drainage.

The intrinsic complications of the pneumonic process (Table 3) were the

TABLE 3. INTRINSIC COMPLICATIONS OF THE PNEUMONIC PROCESS

1. Pleural effusion
2. Empyema
3. Lobar or segmental collapse (atelectasis)
4. Lung abscess

most common causes of protracted resolution in the younger age group. These are closely associated with the factors already discussed. Scadding<sup>5</sup> pointed out that chronic suppurative pneumonia rarely follows pneumococcal pneumonia, but was unable to cor-

relate the bacteriology with the clinical course in his cases. Although pleural effusion is not uncommon in the more severe pneumonias, no case initially treated by us developed empyema.

The major etiological process responsible for delayed resolution was determined in 50 (96.1%) of the 52 cases (Table 4). Many of the older patients

TABLE 4. DISTRIBUTION OF 52 CASES OF DELAYED RESOLUTION ACCORDING TO MAJOR ETIOLOGICAL PROCESSES

|  |    |
|--|----|
| Impaired Bronchial Drainage .....          | 22 |
| Bacteriological and Chemical Factors ..... | 16 |
| <i>Intrinsic Complications of the</i>      |    |
| Pneumonic Process .....                    | 12 |
| Undiagnosed .....                          | 2  |
| Total .....                                | 52 |

presented multiple etiological factors. Each has been classified under the one factor considered largely responsible for the delay in clearing. It is to be noted that in not quite half of our patients impaired bronchial drainage was the significant process causing delay.

A specific organism or chemical insult was responsible for the delay in 16 (30.7%) patients (Table 5). Aspira-

TABLE 5. DISTRIBUTION OF 16 CASES OF DELAYED RESOLUTION OF PRIMARY BACTERIOLOGICAL AND CHEMICAL ETIOLOGY

|                                  |   |
|----------------------------------|---|
| Aspiration of Anerobic Organisms |   |
| of the Oropharynx .....          | 6 |
| Klebsiella pneumoniae .....      | 4 |
| Oil Aspiration .....             | 2 |
| Mycobacterium tuberculosis ..... | 2 |
| Streptococcus .....              | 1 |
| Primary Atypical Pneumonia ..... | 1 |

tion was the most common cause, and 5 of the 6 patients developed single or multiple lung abscesses, 4 of which were removed surgically. Friedlander's pneumonia occurred in 4 patients, all of whom recovered under streptomycin therapy. Of the 2 cases in which delay in clearing was considered secondary

to oil aspiration, one followed the instillation of the iodized oil for diagnostic purposes. The second case was a typical example of lipoid pneumonia in a patient who lubricated his permanent tracheotomy opening with mineral oil several times daily over a period of many years.

Impaired bronchial drainage was responsible for the delay in 22 (42.3%) cases (Table 6). Four of these cases

TABLE 6. DISTRIBUTION OF 22 CASES OF DELAYED RESOLUTION DUE TO IMPAIRED BRONCHIAL DRAINAGE

|  |   |
|--|---|
| Emphysema and Fibrosis .....                           | 5 |
| Bronchogenic Carcinoma .....                           | 4 |
| Arrested Pulmonary Tuberculosis .....                  | 3 |
| Chest Trauma .....                                     | 2 |
| Chronic Bronchitis .....                               | 2 |
| Bronchial Asthma .....                                 | 2 |
| Non-specific Bronchial Stenosis .....                  | 1 |
| Pneumoconiosis .....                                   | 1 |
| Hilar Node Enlargement .....                           | 1 |
| Paralysis of Laryngeal and<br>Pharyngeal Muscles ..... | 1 |

were proven to be due to bronchogenic carcinoma. All 4 of these patients whose early diagnosis and definitive treatment were delayed for some months by treatment for pneumonia proved to be non-resectable and have since died. The other frequent cause of delayed resolution in this group was pulmonary fibrosis and emphysema. The 5 patients with this condition required months for resolution to occur, but finally cleared completely. One of this group has since suffered a second pneumonic episode in the same lung, which again was slow in resolving.

The last group of cases to be con-

TABLE 7. DISTRIBUTION OF 12 CASES OF DELAYED RESOLUTION DUE TO INTRINSIC COMPLICATIONS OF THE PNEUMONIC PROCESS

|                                   |   |
|-----------------------------------|---|
| Lung Abscess .....                | 4 |
| Lobar or Segmental Collapse ..... | 4 |
| (Atelectasis)                     |   |
| Pleural Effusion .....            | 2 |
| Empyema .....                     | 2 |

sidered is that in which delay was caused by intrinsic complications of the pneumonic process itself (Table 7). Twelve patients (23%) fall in this category. These generally consisted of younger patients with extensive lesions, whose treatment was instituted late or who received inadequate initial treatment without adequate bacteriological study. It is possible that the cases listed here as lung abscess might have been more properly classified under other headings if they had been studied in an earlier phase of their disease. The group listed as lobar or segmental collapse is easily the most difficult to evaluate. An element of atelectasis is probably present in all pneumonias. Coryllos and Birnbaum<sup>2</sup> have set forth the concept that lobar pneumonia is a pneumococcic atelectasis due to bronchial obstruction by mucus infected with virulent pneumococci. We have no adequate explanation for the prolonged presence of collapse in these 4 patients, despite active therapy with bronchodilator drugs and bronchoscopic aspiration.

The 2 patients in whom no clear, underlying factor could be demonstrated included a young man with extensive miliary nodular disease of the lungs of undetermined origin. The second case was that of an elderly man with pernicious anemia who suffered an extremely severe lobular pneumonia involving the entire right lung.

It will be noted from this review that in almost every instance of delayed resolution one or more local etiological factors could be found to account for the phenomenon. The most significant finding of this entire study appears to be the fact that of 52 cases of delayed resolution, 4 cases (7.7%) were proven to be due to bronchogenic carcinoma\*. It seems clear, therefore, that bronchogenic carcinoma should occupy a prominent place in the differential diagnosis of delayed resolution in pneumonia. No sounder advice can be offered to the clinician than Amberson's statement<sup>1</sup>, "It should be the inflexible rule of the clinician never to make a diagnosis of unresolved or organizing pneumonia without searching for the cause; otherwise, patients with serious and remediable lesions of the lungs may miss the opportunity of early diagnosis and cure."

Summary. 1. The major etiological factors producing delayed resolution in pneumonia have been determined in 50 (93.1%) of 52 cases studied.

2. The major process responsible for delayed resolution was found to be impaired bronchial drainage in 22 cases (42.3%); in 4 cases, this was directly the result of bronchogenic carcinoma. A specific organism or chemical insult was responsible in 16 cases (30.7%). Intrinsic complications of the pneumonic process caused delayed resolution in 12 cases (23%).

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\* Since the compilation of this report 3 more patients have been studied who were treated for pneumonia for varying periods, and who have been proven to have bronchogenic carcinoma as the etiological factor.

# THE TREATMENT OF FALCIPARUM MALARIA WITH INTRAMUSCULAR CHLOROQUINE

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CULWELL *et al.*<sup>6</sup> have recently demonstrated the efficacy of intramuscular chloroquine in 16 cases of sporozoite induced, Chesson strain, *vivax* malaria. The antimalarial action of the drug was comparable to that resulting from oral administration and no toxic reactions were observed. When given orally chloroquine has been found to be highly effective in the treatment of all types of malaria<sup>4-6,8,10-12</sup> and the toxicity less than that following quinine or quinacrine administration<sup>1,2,4,7,10</sup>.

There is no report of *naturally* acquired falciparum malaria treated with parenteral chloroquine. We have treated 8 patients with falciparum malaria with chloroquine intramuscularly. All of these patients acquired their infection in Africa and 6 had received suppressive or therapeutic quinacrine or quinine prior to admission to the hospital. The longest period that elapsed between the last administration of antimalarial drugs and treatment with parenteral chloroquine was 42 days; the shortest was 12 days. After the diagnosis was confirmed by blood smear each patient was given an intramuscular injection of 0.2 gm. of chloroquine base in 5 cc. of sterile unbuffered aqueous solution according

to the method of Culwell *et al.*<sup>6</sup>. One patient (Case 8) received an additional dose of 0.2 gm. intramuscularly 3 days after initial administration of the drug. Daily parasite counts were done on each patient and 2 to 5 days later each patient was given a routine course of oral chloroquine as recommended by Most *et al.*<sup>10</sup>. Results of treatment are summarized in Table 1.

No adverse local or systemic effects from the intramuscular chloroquine were observed in any of these patients; toxic effects following the parenteral administration of quinine or quinacrine are not infrequent. Rapid clearing of the parasites from the peripheral blood occurred although none of the patients had very high initial parasite densities. The most striking feature of treatment with parenteral chloroquine in this series was that in 6 of the 8 patients no asexual falciparum parasites were found in the blood after administration of the initial dose. The remaining 2 patients showed only 30 and 60 ring forms on the morning of the day further therapy was given. It is likely that the blood of these patients would likewise have cleared completely if further therapy had been delayed. Four of the 8 patients showed

gametocytes in their smears after their blood was free of asexual parasites. Neither the intramuscular nor oral chloroquine had any apparent effect on the sexual forms.

The clinical response of these patients to intramuscular chloroquine was likewise very striking. All of them became completely afebrile in 1 to 2 days and were markedly improved subjectively. Nausea and vomiting which had occurred in 3 patients subsided promptly following the initial therapy.

The effect of previous antimalarial medication in these patients cannot be

of the patients had symptoms of cerebral malaria nor were any in coma. Culwell *et al.*<sup>6</sup> pointed out that none of the patients treated by them were critically ill and that it was impossible to conclude from their series that chloroquine given intramuscularly would prove rapidly efficacious in overwhelming infections where there is peripheral vascular stasis. Since none of our patients were critically ill, either, no definite conclusions can be reached as to the route of administration of the drug in this type of patient. Culwell *et al.*<sup>6</sup> suggested that chloroquine could

TABLE 1.—CLINICAL AND PARASITOLOGICAL RESPONSE IN 8 ATTACKS OF NATURALLY ACQUIRED FALCIPARUM MALARIA TREATED WITH INTRAMUSCULAR CHLOROQUINE

| Case Number | Attack Number | Parasite count per cu. mm. on day of therapy | Parasite count on second day | Parasite count on third day | Parasite count on fourth day | Parasite count on fifth day | Parasite count on sixth day | Days to negative smear (for asexual forms) | Days until afebrile <37.0°C (<98.6°F.) |
|-------------|---------------|--|------------------------------|-----------------------------|------------------------------|-----------------------------|-----------------------------|--|--|
| 1           | 2             | positive (no count made)                     | 9,720                        | 3,000                       | —                            | 0                           | —                           | 4  | 1                                      |
| 2           | 3             | 6,380  | 1,330                        | 0                           | 0                            | —                           | —                           | 2  | 1                                      |
| 3           | 1             | 7,080  | 300                          | 60                          | 0                            | —                           | —                           | 3  | 2                                      |
| 4           | 1             | 20,750                                       | —                            | 2,457                       | —                            | 30                          | 0                           | 5  | 1                                      |
| 5           | 2             | 9,590  | 5,400                        | 420                         | 0                            | 0                           | 0                           | 3  | 2                                      |
| 6           | 1             | 6,120  | 2,530                        | 0                           | 0                            | 0                           | 0                           | 2  | 1                                      |
| 7           | 3             | 1,560  | 490                          | 60                          | —                            | 0                           | 0                           | 4  | 2                                      |
| 8           | 3             | 19,500                                       | 14,630                       | 4,190                       | 0                            | 0                           | 0                           | 3  | 1                                      |

definitely determined. It is not likely, however, that this medication had any effect on their response to intramuscular chloroquine since there was a period of from 12 to 42 days from the time the patients last took quinine or quinacrine until chloroquine was given.

It has been recommended that malaria with persistent vomiting, coma, impending coma or a high density of falciparum parasites in the blood smears (5% or more of red cells infected) be treated with parenteral antimalarial drugs<sup>3</sup>. Although none of the patients in this series showed a high parasite density, 3 of them had nausea and vomiting severe enough to prevent administration of oral medication. None

be given in a saline infusion intravenously over the course of 3 to 4 hours for the treatment of patients critically ill with falciparum malaria as carried out by Machella *et al.*<sup>9</sup> with quinacrine and SN 6911. The parenteral administration of chloroquine is not recommended for patients who can take the drug by mouth except for those who show very high parasite densities<sup>3</sup>, as the absorption of chloroquine from the alimentary tract is usually very rapid.

The following case history illustrates the type of response obtained with intramuscular chloroquine in this series:

Case Abstract—CASE 5. S. C., a 32 year old seaman was admitted to the hospital on



September 18, 1948, complaining of chills and fever. About 2½ months before admission he had sailed for Africa. Three days before arriving in Africa, about 2 months before admission, he began to take a capsule of quinine daily. He did not know the amount of quinine in the capsule. His ship touched various ports along the west coast of Africa during a period of about 1½ months. The patient was ashore in many of these ports in the evening and overnight. He continued to take quinine but, about 15 days before admission, he had onset of chills, fever, nausea, and vomiting. At this time he was seen by a phy-

about the orbit, the result of an old injury, physical examination was essentially negative.

Laboratory examinations showed that the hemoglobin was 12.0 gm., red cell count 3,800,000, white cell count 7,500 (68% neutrophils, 22% lymphocytes, 8% monocytes, and 2% eosinophils). The Kahn precipitation test and Cardio-Lipin test were negative. Smears were positive for plasmodium falciparum.

After admission the patient's fever continued, although on one occasion it dropped to normal (Fig. 1). About 36 hours after admission, the patient had a chill, nausea, and vomiting, and his temperature rose to

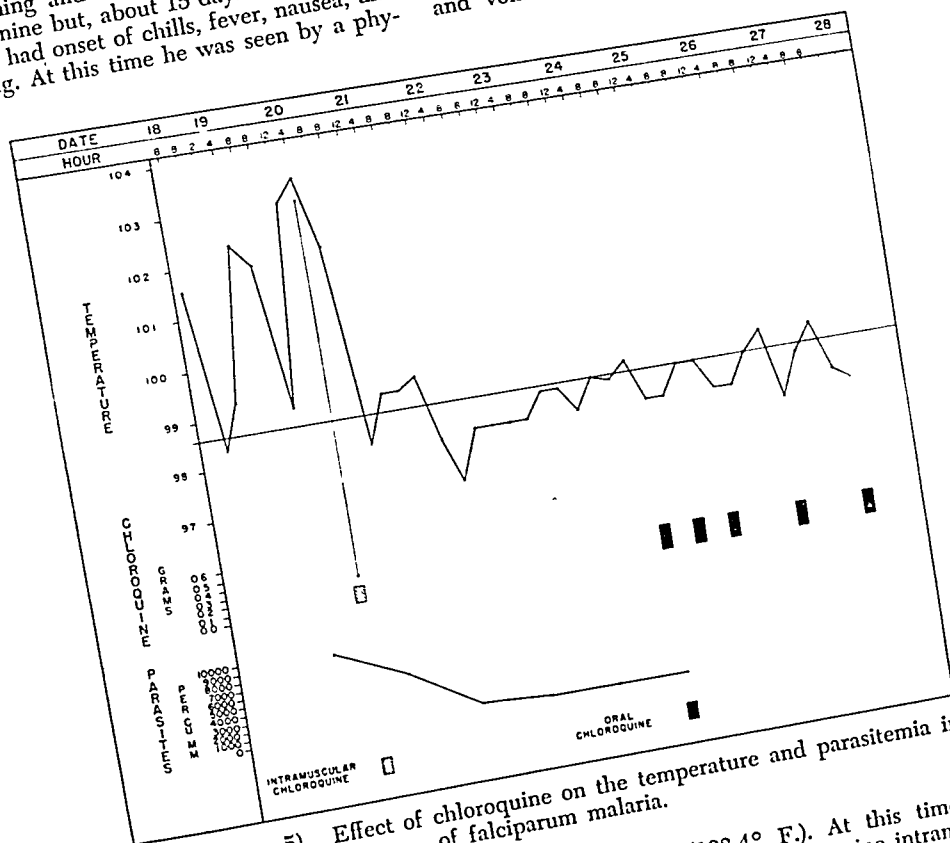


Fig. 1. S. C. (Case 5). Effect of chloroquine on the temperature and parasitemia in a case of falciparum malaria.

sician in the Canary Islands. His quinine was discontinued, and he was given some "white pills" by the physician. He was incapacitated for 5 days, but after this resumed his duties and felt well until the day before admission when he again had chills, fever, nausea, and vomiting.

Physical examination on admission showed a well developed and nourished white male in no acute distress. His temperature was 39.7° C. (101.5° F.), pulse 100, and blood pressure 115/80. Except for a deformity

39.5° C. (103.4° F.). At this time he was given 0.2 gm. of chloroquine intramuscularly. Within 40 hours the patient had become afebrile and felt well. He had no complaints and remained essentially afebrile during the rest of his hospitalization. His smears became negative for malarial parasites in 2 days, and remained negative. Seven days after admission (5 days after parenteral administration of chloroquine) oral chloroquine was begun. He received 1.5 gm. of chloroquine base in 4 days. He was discharged from the hospital on September 28, 1948.

- Summary. 1. Eight patients with naturally acquired falciparum malaria were treated with intramuscular chloroquine. to treatment and there was rapid clearing of the asexual parasites from the blood.
2. All of the patients responded well 3. No local or systemic toxic effects from the drug were observed.

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## LOCALIZED SEALED-OFF PERFORATION IN RECURRENT DUODENAL ULCER

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ACUTE perforation of a peptic ulcer usually produces a typical clinical picture that offers little diagnostic difficulty. There is usually "an acute surgical abdomen" with free gas in the peritoneal cavity. The free gas is demonstrated beneath both domes of the diaphragms in the majority of cases. Another variety of perforation is the "Formes Frustes" reported by Singer and Vaughan<sup>1</sup>. In the latter condition an acute surgical condition is present in the abdomen, often with free air in the peritoneal cavity. This subsides after a number of hours, leaving the patient in comparative comfort. In both varieties of perforation there is acute abdominal pain, prostration, shock, and a board-like rigid abdomen. In the type of sealed-off perforation reported here, severe symptoms and shock were absent, the patients were ambulatory. There is no free air in the peritoneal cavity.

There are 3 types of walled-off perforations: 1, a medical type; 2, a surgical type; and 3, chronic perforation with an accessory pocket. Only the first variety will be discussed in this communication. Five such cases are here reported.

The sealed-off medical variety of perforation must occur with greater frequency than is suspected. This complication, although mild, has not often been recognized. There is a dearth of information on this type of perforation complicating the ambulatory case of duodenal ulceration. The actual incidence has never been com-

puted, probably because sealed-off perforations of this type are best demonstrated by special methods of examination. Within a 3 months' period, approximately 65 cases of duodenal ulcer in all stages were examined. Among these there were 5 of this form of perforation. These patients presented clinical symptoms which were more pronounced and lasted longer than any the patient had previously experienced. Although this is too brief a period and too small a series to establish its incidence, it is nevertheless possible to demonstrate its existence and emphasize the frequency of this condition. Since these cases represented a selected group, the true incidence cannot as yet be established. If one would examine all intractable duodenal ulcer cases, in the erect position, utilizing the spot film compression technique, many cases of sealed-off localized perforations would be detected. The 5 cases of recurrent duodenal ulcer presented in this communication had been selected for spot film examination because of their clinical history of an abrupt onset of an unusual mild digestive episode.

The subhepatic gas-bubble is not a new sign for walled-off perforations. Attention is now being directed to a pinpoint sealed perforation of a medical type, its incidence and the roentgenologic method to demonstrate them.

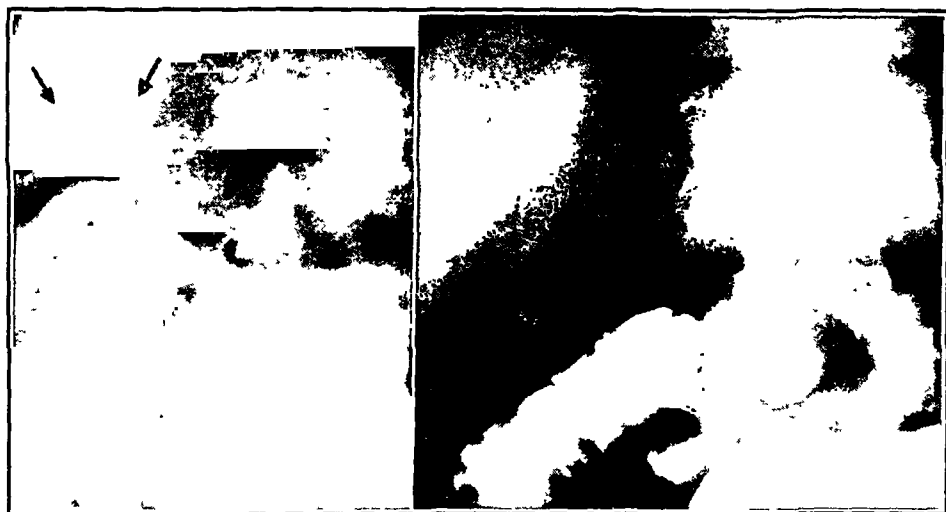
The following 5 cases are presented to show the characteristic clinical and roentgen picture of a medical type of walled-off minimal pinpoint perfo-

ration which had spontaneously sealed itself.

**Case Reports.** **CASE 1.** A man, aged 52, first had an ulcer 25 years ago. At intervals since then there were complaints of epigastric pain, relieved by food, which awakened him during the night. He felt well, with few symptoms, until about 1 year ago, when he began to have symptoms refractory to the usual treatment. Recently he had an acute episode that differed from any experienced before. The usual ambulatory treatment did not give complete relief. Roentgen-ray examination revealed a markedly deformed duodenal bulb with an ulcer-niche filling defect. Situated above the duodenal bulb and outside the duodenal contour was a persistent localized small air-pocket. This was

to be adherent by extensive adhesions beneath the liver. There was evidence of chronic inflammatory changes involving the serosa and a matting together of adjacent tissues surrounding the suspected old pinpoint perforation. The duodenal bulb revealed evidence of a chronic ulceration. Arising from the inner aspect of the bulb, there was a pseudo-diverticulum or an accessory pocket of a perforation which was not observed in the previous roentgen examination.

**CASE 2.** Man, aged 48, had recurrent symptoms of a duodenal ulcer for 15 years. Frequent follow-up examinations showed complete healing and cicatrization of the ulcer, with varying degrees of gastric retention. Until recently, he had few symptoms and no changes in the anatomic appearance of the healed ulceration. In a recent episode



**FIG. 1. CASE 1.** (A) Roentgenogram made in the erect position with spot film compression. A markedly deformed duodenal bulb with a large air-bubble above the duodenum is shown at arrows. Note the flattened base of the air-pocket, due to a small amount of fluid. (B) Same case, with roentgenogram made in the recumbent prone position without compression. No gas pocket can be demonstrated.

demonstrated only in the erect position. A diagnosis of a minute blowout type of walled-off perforation was made. He was hospitalized at the Church Home Hospital for a few weeks and obtained complete relief of symptoms. Re-examination made 3 and again 11 months later did not show any sign of perforation. The encapsulated air-pocket had disappeared.

This patient remained clinically well for almost 1 year, when his ulcer symptoms recurred. Because of the repeated episodes of the intractable ulcer, he was re-admitted to the Church Home Hospital for surgical exploration. At operation the duodenum was found

there was a recurrence of symptoms that lasted longer than any he had experienced before. Roentgen-ray examination at this time showed a recurrence of activity with an ulcer niche defect. There was about a 10% gastric residue in 5 hours. A small air-bubble was demonstrated directly above the duodenal bulb which was due to a recent pinpoint sealed-off perforation. This encapsulated air was only seen in the erect position. No barium was seen to enter the pocket. A diagnosis of a sealed-off perforation of a duodenal ulcer was made, which accounted for the recurrence of atypical symptoms.

This patient returned for re-examination 6

months later. At this time he had no digestive symptoms and felt comparatively well. A check-up examination showed that the ulcer niche and the gas-bubble had disappeared.

CASE 3. A 53 year old man had stomach trouble for 10 years, with periodic pains relieved by food, characteristic of duodenal ulcer. Recently his symptoms suddenly became worse, and were different from any he had had before. They were more severe and lasted longer than in any other previous attack. The spell was not severe enough to keep him from working, although the vomiting had weakened him considerably. He had never vomited before this episode. Roentgen-ray examination revealed evidence of a

tite was good. There was no loss of weight. Roentgen studies of the gastrointestinal tract at this time revealed a duodenal ulceration. Three years later a gallbladder study revealed a large number of small gallstones. He was operated upon 1 year ago and the gallstones were removed; this was followed by complete relief from his acute abdominal attacks. About 6 months later his ulcer symptoms suddenly recurred, with abdominal pain, which awakened him during the night. A gastrointestinal study made at this time revealed a pyloro-duodenal deformity due to an ulceration, associated with a redundant prolapsing gastric mucosa. A small gas-bubble was observed above the superior aspect of the



FIG. 2

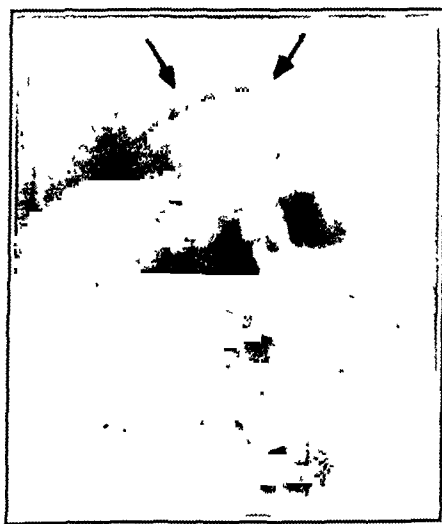


FIG. 3

FIG. 2 CASE 2. Demonstrates a deformed contracted cap with an ulcer niche defect at arrow. Note the air-bubble with a flattened base, atop the bulb at arrows.

FIG. 3. CASE 3. An elongated deformed duodenal bulb is shown. Note the small subhepatic air-bubble above the duodenal bulb at arrows.

duodenal deformity with an ulcer-niche defect. A small encapsulated air-pocket was demonstrated above the duodenal bulb, only in the erect position. The diagnosis of a minute blowout type of walled-off sealed perforation was made.

CASE 4. A man, aged 40, had coronary heart disease for 6 years. His onset of digestive trouble began 5 years ago with attacks of abdominal pain, without food relation. The pain was severe, radiating between the shoulder blades, requiring morphine for relief. Between the attacks he felt well. His appe-

duodenum. This suggested a recent escape of a small amount of air from a pinpoint perforation which had spontaneously sealed itself, and became walled off in the subhepatic area.

CASE 5. A man, aged 49, had digestive trouble for 15 years. The predominant symptoms were pyrosis and pains across the upper abdomen. His appetite was good and he always felt better when he ate. He had an appendectomy without relief and later a gallbladder operation. The last digestive episode began 1 week before admission with epi-

gastric distress and pain. There was no food relief. Ordinary treatment did not help him as it had before. Because this spell of indigestion lasted longer than usual, he sought medical attention. A gastrointestinal Roentgen-ray examination revealed a deformed duodenal bulb due to an ulceration. No ulcer niche defect could be demonstrated. Atop the duodenal bulb, the erect compression spot film showed a persistent small air-bubble about the size of a chestnut. A diagnosis of recurrent duodenal ulceration with a sealed-off perforation was made.

**Discussion.** Clinically, this form of perforation more commonly occurs in cases of recurrent duodenal ulceration.

There is usually persistent pain in the epigastrium, somewhat to the right of the mid-line. The pain lasts longer than usual, tends to become milder and intermittent. Later there is a persistent soreness and discomfort in the epigastrium. At times food increased the discomfort. Vomiting frequently occurred during the episode.

Five ambulatory cases of a pinpoint, spontaneously sealed-off type of perforation occurring in recurrent duodenal ulceration were observed. The symptoms presented were not severe,



FIG. 4

FIG. 4. CASE 4. Illustrates a small gas-bubble atop the duodenal bulb. The amount of air in the gas pocket is minimal, could only be demonstrated on the erect spot compression films.



FIG. 5

FIG. 5. CASE 5. A markedly deformed duodenal bulb with a small subhepatic air-bubble shown at arrows.

The attacks are usually mild and transient. In most instances the symptoms are more exaggerated but the possibility of a perforation is not ordinarily considered. These patients do not obtain relief with food, soda or antispasmodics as quickly as they had previously. The patient is of the opinion that a new condition has occurred for which he seeks medical

but differed from those the patients had previously experienced. All of the 5 cases were males. There was an ulcer deformity of the cap in all of the cases and in 3 an ulcer niche defect was demonstrated. In all 5 cases there was a small, well defined encapsulated air-bubble situated above and outside of the duodenal bulb. All of these cases presented a persisting digestive episode.

The duration of their ulcer symptoms ranged from 5 to 25 years.

This type of perforation in which there is an abrupt or insidious pinpoint blowout with spontaneous sealing-off of the perforation and walling off of the adjacent tissues, is thought to account for the subhepatic air-bubble. Occasionally, a small amount of fluid capped with air is seen in the base of the pocket. These perforations must be of pinpoint size permitting only air to escape. In none of the cases of this form of perforation had the barium meal escaped into the pocket. It is interesting to point out that the gas-bubble with a minimal amount of air was only demonstrated in the erect position under compression, while in the recumbent position no air pocket was observed. The gas-bubble in these cases could not be clearly demonstrated under the fluoroscope in any position. No communication was seen between the ulcer and the encapsulated air-pocket. The gas-bubble is generally small, smooth in contour with its superior aspect dome-shaped and its base flat above the duodenal contour. The similarity of the clinical manifestations and the Roentgen-ray picture of a subhepatic gas-bubble in all of the 5 cases was a striking feature. The gas-bubble usually disappears within a few weeks of treatment.

Multiple perforations may occur in some patients. How many sealed-off perforations occur during the life cycle of a case of duodenal ulceration is not known. However, it is most likely that multiple perforations of this type do occur in some instances. In Case 1, there were 2 perforations: a pinpoint sealed type, and later an accessory pocket type.

The purpose of this communication is to give information regarding a medical type of perforation that has not been demonstrated before. The following fundamental data are pre-

sented: 1, pinpoint leak-type perforations not uncommonly complicate chronic recurring duodenal ulceration; 2, it is associated with an active duodenal ulceration; 3, the subhepatic gas-pocket is an abnormal finding; 4, the gas-pocket is a roentgenologic observation.

The type of perforation considered in this paper was of a mild and transient nature presenting a medical problem. In 1 of the 5 cases there was surgical confirmation of the condition. Gas pockets outside of the duodenum are normally not observed unless there is a perforation, an air filled diverticulum or overshadowing gaseous viscus. The gas pocket in these cases cannot be considered as trapped air within the duodenum as it is distinctly outside of the duodenal contour. Because of the minimal amount of air which escapes from the pinpoint duodenal perforation, the condition is best demonstrated in the upright position. In the type of perforation discussed no barium entered the sac. The amount of air visible within the gas pocket depends upon the stage and time interval following the perforation. This small amount of air and, occasionally, fluid is usually absorbed, leaving no Roentgen evidence of the condition in later examinations.

In the differential diagnosis, other subhepatic gaseous shadows must be eliminated. The following conditions should be differentiated: 1, gas in a loop of colon (hepatic flexure); 2, gas in a loop of duodenum, such as is found in an inverted duodenum; 3, subhepatic abscess; 4, emphysematous cholecystitis. These conditions are ordinarily easily eliminated by the proper special type of examination.

**Conclusions.** 1. A medical type of localized, spontaneous, sealed-off pinpoint perforation as a complication of duodenal ulceration is described.

2. The possibility of a sealed-off pin-

point type of perforation of a duodenal ulcer should be looked for in all recurrent ambulatory cases presenting symptoms which are more severe or unusual.

3. The incidence of this variety of walled-off perforation is probably greater than has been suspected.

4. In this form of perforation a small gas-bubble in the subhepatic area above and outside of the duodenal contour may be recognized.

5. It is generally associated with a recurrent active duodenal ulcer with a demonstrable niche defect.

6. The air-pocket frequently contains a small amount of exudate or fluid. No barium entered the pocket in the cases presented.

7. The subhepatic gas-bubble is best demonstrated on spot films in the erect position, utilizing the compression technique.

8. Five cases are presented, of walled-off sealed pinpoint type of perforation occurring in recurrent chronic duodenal ulceration. One of these was surgically explored and proved to have had a perforation.

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# CO-EXISTENT HODGKIN'S DISEASE AND KAPOSI'S SARCOMA

## REPORT OF A CASE WITH UNUSUAL CLINICAL FEATURES

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This case of Hodgkin's Disease is presented because of: a) the co-existence of Kaposi's Sarcoma, a rare and apparently unreported occurrence, and b) certain unusual clinical features.

Case Report. M. P., a 54 year old white male, was first seen by one of us (RHG) on October 18, 1946. He had been on a reducing diet for 1 year, but despite stopping the diet had continued to lose weight for 2 months, and felt weak. On examination, his weight was 182 pounds, the blood pressure was 150/80, the heart and lungs showed nothing noteworthy and a large, left upper quadrant abdominal mass was felt and thought to be spleen. No enlarged lymph nodes were palpated. The following day he was admitted to the hospital for diagnostic study. The physical examination showed no additional findings. The following laboratory studies were obtained: Hemoglobin, 10.7 gm. (74%); red cell count, 3,690,000; white cell count, 4,000 (62% segmented neutrophils, 6% non-segmented neutrophils, 25% lymphocytes, 4% monocytes and 3% young forms); platelet count, 180,000, bleeding time, 2 minutes; coagulation time, 5 minutes; blood sugar 104 mg.%; blood urea nitrogen 13 mg.% prothrombin time 100%; Total proteins 5.9 gm.%; Blood uric acid 4.8 mg.%. A fragility test showed hemolysis beginning at 0.44 and complete at 0.32. An aspiration biopsy of the sternal marrow revealed no evidence of a leukemic process.

Roentgen studies of the chest, urinary tract, gall bladder, upper gastrointestinal tract, colon and long bones revealed only some evidences of gastritis and duodenitis and old tuberculous foci in the lungs. No mediastinal adenopathy was demonstrated. A urinalysis for Bence-Jones protein was negative. An adrenalin test did not produce abnormal cells in the peripheral blood.

Because of the mild anemia and weakness,

a blood transfusion was given. A splenic puncture was contemplated, but not performed. The patient was discharged with a diagnosis of "Splénomegaly of undetermined origin," and seen subsequently as an out-patient. In December, 1946, Roentgen therapy to the spleen resulted in a decrease in size of that organ and a rise in hemoglobin to 94%. The following month, a few enlarged cervical lymph nodes were noted. From a biopsy of one of these (Dr. David R. Meranze) "Lymphoblastoma, probably Hodgkin's Disease" was diagnosed.

Beginning in March, 1947, the patient's disease process gradually became more active, establishing a need for blood transfusions and Roentgen therapy. This supportive therapy not being helpful, the patient was re-hospitalized in June, 1947. A high fever developed and the anemia and leukopenia became more severe. The white blood cell count varied from 1200 to 2000 with 5 to 15% neutrophils. He developed gingival and rectal ulcerations. The rectal lesions progressed to an abscess which required incision. These lesions were kept under some control with penicillin and streptomycin. The anemia, however, was unrelieved by numerous transfusions.

At this time (July, 1947), despite the extreme neutropenia, nitrogen mustard therapy was instituted (20 mg. in 4 days). The response was dramatic, with an immediate subsidence of fever. The mucosal lesions healed rapidly, although no change was noted in the white cell count. Blood transfusions were now effective in bringing his hemoglobin and erythrocyte count to a more tolerable level.

During this admission, he first began to complain of pain in his toes and feet. An infiltrative skin lesion was noted, consisting of erythematous scaling papules involving predominantly the toes and the tibial crests. This lesion was not affected by the nitrogen mustard therapy—the lesions and associated pain

remaining, although the general symptomatology was markedly improved by the drug. No skin biopsy was taken. The clinical impression was that of either Hodgkin's cutaneous infiltration or Kaposi's Sarcoma.

From July, 1947, until his death on February 23, 1948, the patient received 5 courses of nitrogen mustard therapy, and numerous blood transfusions. During each remission, which lasted on an average of 4 to 5 weeks, there was disappearance of fever, improved appetite, and a rise in the hemoglobin level.

In September, 1947, an interesting hematologic development was noted. The white cell count, which had previously averaged 2000, rose suddenly to 6000 and then to 10,000. At that time there appeared in the peripheral blood many primitive cells of the monocytic type, numbering 60 to 70% of the total white cell count. Within a few days the numbers of these cells diminished rapidly and the leukocyte count dropped to 3000. Death occurred on February 23, 1948, during the eleventh hospital admission.

*Autopsy* (9 hours after death). The body appeared moderately emaciated, with slight cyanosis and scleral icterus. There was abdominal distension, with moderate edema of the legs and ankles. The toes, feet and pretibial regions showed the presence of numerous raised, flat, greyish-purple nodules, averaging 4 to 7 mm. in diameter and 1 to 2 mm. in height. Many of these showed a tendency to confluence and most showed slight scaling. The superficial lymph nodes were not palpably enlarged.

There was a left pleural effusion of 1200 cc. and 7200 cc. of fluid in the abdominal cavity. Marked perisplenic adhesions were present. A mass of conglomerate lymph nodes, varying from 1.0 to 3.5 cm. in diameter was present in the right anterior superior mediastinum. A mass of similar nodes was noted at the right lung hilum. The lungs showed moderate edema and congestion, with small foci of bronchopneumonia. Numerous small subpleural nodules, less than 1.0 cm. in diameter, were present. An old, fibro-calcareous lesion (tuberculous) was noted at the right lung apex.

The heart weighed 330 gm., was slightly dilated and showed slight coronary sclerosis. The gastrointestinal tract was essentially negative. The mesenteric lymph nodes were slightly enlarged. The liver was moderately enlarged, weighing 2550 gm., and showed alternate areas of swollen and collapsed lobules, with small hemorrhagic foci. There was slight cholesterosis of the gall bladder mucosa.

The spleen was markedly enlarged, weighing 2120 gm. and measuring 28.0 x 18.0 x

9.0 cm. The capsule showed irregular areas of thickening, beneath which were seen large, sharply-demarcated, yellowish-grey infarcts. The pulp was soft, dark-red and mottled. The central areas were slightly diffuent, probably due to incomplete fixation.

The kidneys were slightly enlarged, having a combined weight of 440 gm. They showed slight surface granularity, with small superficial retention cysts. The pancreas, adrenals, urinary bladder, prostate and testes were not remarkable. The brain was not examined.

*Histologic examination* revealed extensive Hodgkin's lesions, involving the spleen, lymph nodes, sternal, rib and vertebral marrow and with small pulmonary and renal infiltrations. In addition, the bone marrow showed an essentially normal cellularity, with apparently normal maturation processes of the myelogenous and erythroid elements. Sections of the skin lesions revealed neoplastic areas in the corium consisting of small, irregular blood vessels in a reticular and fibroblastic framework. Erythrocytes were present in the vessels. Similar lesions were noted in areas of the lung, isolated from the Hodgkin's lesions, and in a few lymph nodes. These secondary lesions showed a marked tendency to produce a more fibroblastic picture. Large angiomatous spaces were also seen in the spleen in the vicinity of the infarcts. However, these were considered to be peculiar reactive changes rather than neoplastic. The liver showed an extensive subacute necrotizing hepatitis.

The *pathologic diagnoses* were: 1) Hodgkin's sarcoma of spleen, lymph nodes and bone marrow, with pulmonary and renal infiltrations; 2) cutaneous angio-endothelioma (Kaposi's sarcoma), with lymph node and pulmonary metastases; 3) massive ascites; 4) necrotizing subacute hepatitis; 5) cardiac failure with pulmonary edema and congestion; 6) terminal bronchopneumonia.

**Comment.** This case offers several avenues for discussion, from both the pathologic and the clinical viewpoints. Although a number of instances have been cited of the co-existence of Kaposi's sarcoma and leukemia<sup>1,2,3</sup> or lymphoblastoma<sup>4</sup>, we have found no cases reported in which there was present Hodgkin's disease and Kaposi's sarcoma. Our review was based on the Quarterly Cumulative Index Medicus as a source of reference. Such cases, to be sure, have been seen, according to

Erf<sup>6</sup> and Wolf (in a discussion of a case presentation by Rosen<sup>1</sup>).

If we are to consider these 2 lesions (Hodgkin's disease and Kaposi's sarcoma) as being primarily of reticulo-

other lymphoblastomas and their variants and leukemia, and the appearance of one or another of the lymphoblastomas in successive examinations in the same patient has been frequently noted.



FIG. 1. Lymph node. Hodgkin's Disease (x 650).

FIG. 2. Bone Marrow (vertebral). Normal area (x 90).

endothelial origin, their association should not be coincidental. Numerous workers (reviewed by Custer and Bernhard<sup>6</sup>) have commented upon the interrelationship of Hodgkin's disease, the

Willis<sup>7</sup> suggests that Kaposi's sarcoma may be a variant of the lymphoblastomas, with prominent skin lesions related to those of Hodgkin's disease and mycosis fungoides. However,

Aegerter and Peale<sup>8</sup> feel that Kaposi's sarcoma originates in the angioblasts, and that this condition is a variant of angiosarcoma.

On the other hand, Symmers<sup>9</sup> regards

trauma. According to this opinion, the co-existence of Hodgkin's disease and Kaposi's sarcoma should be interpreted as an unrelated coincidence.

It is our belief that the two conditions



FIG. 3. Subcutaneous tissue. Kaposi's Sarcoma (x 75).

FIG. 4. Lymph node. Kaposi's Sarcoma (x 150).

Kaposi's sarcoma as a type of fibrosarcoma in which the seeming vascular spaces are pseudo-sinusoids and the erythrocytes are extravasated into these spaces from nearby capillaries by

present in the case reported are histogenetically related and that possible other coincident occurrences of these 2 lesions have not been fully appreciated and recorded.

In considering briefly the kindred nature of the lymphoblastomas, leukemia and Hodgkin's disease, it might be interesting to comment on one of the clinical features of this case. We refer to the transient rise in total leukocyte count (to 10,000 cells per c. mm.) with the appearance in the peripheral blood of large numbers (60 to 70%) of primitive mononuclear cells. These cells were similar to those noted in small numbers in the blood at the time of the first admission, and also to cells noted in the vascular spaces of the lymph node taken at the original biopsy. These cells probably arose from the reticulo-endothelial system, being released into the blood stream from active foci of Hodgkin's disease. This temporary abnormal leukocytosis, if viewed as an isolated finding in a patient with splenomegaly, could be diagnosed as leukemia. Custer and Bernhard<sup>6</sup> have reported various transition stages histologically between Hodgkin's or reticulum cell sarcoma and monocytic leukemia. It is only the changing clinico-pathologic picture which reveals the true diagnosis.

Finally, it is felt that some comment should be made upon the use of nitrogen mustard in this case. Although it is

known to induce remissions in Hodgkin's disease, use of this drug has also resulted in severe depressions of the cellular elements of the bone marrow. Therefore its use where leukopenia is present should be regarded as fraught with danger. Despite a leukocyte count averaging 1000 to 2000 with marked neutropenia, however, and with full realization of the dangers, therapeutic dosage of nitrogen mustard therapy was attained. This resulted in no change in the leukopenia but produced dramatic clinical improvement, including healing of the agranulocytic mucosal lesions. This would suggest that this drug might be tried in a susceptible disease process even in the face of a marked leukopenia.

**Summary.** 1. A case of co-existent Hodgkin's disease and Kaposi's sarcoma is presented, no previous case having been found by us in an extensive search of the literature.

2. The possible relationship of these 2 disease processes, together with the lymphoblastomas and leukemias, is briefly commented upon.

3. The use of nitrogen mustard therapy in susceptible disease processes in the face of leukopenia is suggested.

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# THE MURMURS OF CARDIAC ANEURYSM

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THE clinical diagnosis of ventricular aneurysms has depended chiefly upon roentgenological methods. In a small number a permanent bulging of the ventricular border is demonstrable in a chest film or by fluoroscopy. In a larger number of cases even careful examination fails to reveal any deformity of the cardiac border, although careful fluoroscopy or fluorocardiography may give evidence of a systolic expansion of the ventricular wall<sup>5</sup>.

The antemortem diagnosis of a partial cardiac aneurysm can, however, be made in many cases on the basis of physical signs alone. For this reason the evaluation of any sign of diagnostic importance is worthwhile.

One of the most outstanding, though inconstant, findings is the presence of an abnormal cardiac pulsation in an unusual position; in most cases this is noted mesial and craniad to the area of the apex beat. The pulsation may appear within 6 days after a myocardial infarction<sup>13</sup> and soon reaches its maximum intensity. Sometimes it disappears as the connective tissue scar develops and shrinks, but ordinarily it persists for life.

Auscultatory signs of partial cardiac aneurysm were described early. A strong abnormal cardiac pulsation with weak peripheral pulses and distant heart sounds was considered to be a syndrome characteristic of a car-

diac aneurysm<sup>1,6</sup>. In addition, gallop rhythm<sup>11</sup> and murmurs have been described. Aran<sup>1,3</sup> quotes Gendrin who found a "murmur double à temps séparés"; a dry ("sec"), sibilant systolic murmur was followed by a shorter, rougher ("rugueux") diastolic one. These murmurs could not be attributed to a mitral stenosis or to an insufficiency of the aortic valves. A systolic and a diastolic murmur were also reported by Paul<sup>9</sup> in a case of cardiac aneurysm. In a patient in whom the clinical diagnosis of a ventricular aneurysm was made, Remlinger<sup>10</sup> found a systolic and a diastolic musical murmur over a circumscribed area about 2 cm. above and lateral to the xiphoid process. These murmurs sounded as if an "ou" were followed by an "e". The murmurs gradually diminished in intensity, presumably because the aneurysm filled with thrombi. Autopsy revealed a partial cardiac aneurysm the size of a tangerine on the anterior wall of the left ventricle with a diameter of 5 cm. at the orifice. It was partly filled with layers of thrombi. Finally, Kasem-Beck<sup>4</sup>, in a 63 year old man with a cardiac aneurysm the size of an apple above the apical area of the left ventricle, heard a presystolic murmur which, in combination with a dull first and an accentuated basal second sound, led to the wrong *intra vitam* diagnosis of mitral stenosis.

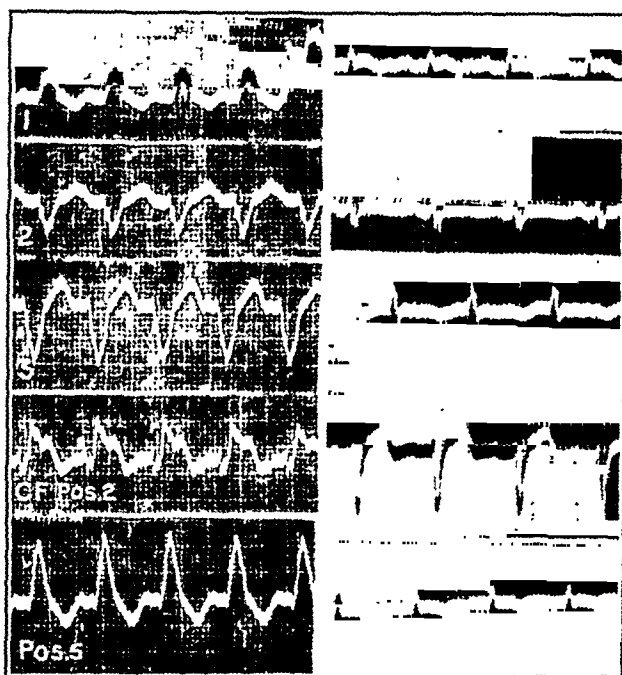


FIG. 1. CASE 1. Fig. 1a shows the electrocardiogram on admission; Fig. 1b was obtained 7 weeks later.



FIG. 2. Cardiac aneurysm on the left border.

In recent reviews<sup>2,8</sup> on the subject, dealing with a larger number of cases, the absence of abnormal murmurs is specifically mentioned. For this reason, and because these murmurs have not been registered with the stethogram, as far as we know, we decided to publish the following 3 recent personal observations. This seems particularly advisable since the presence of the diastolic murmur may lead to the erroneous diagnosis of other cardiac lesions, as will be pointed out later.

**Case Reports.** CASE 1: J.B., a 69 year old colored woman, experienced on April 20, 1948, severe epigastric pain which was constant, dull, and of great intensity. It was accompanied by vomiting, and lasted for 5 hours until an injection of morphine brought relief. The blood pressure fell from 132/90 to 80/60. The white cell count was 10,500; the temperature rose no higher than 99.9°. In the past history the existence of a chronic duodenal ulcer was related. The patient acknowledged syphilis in her youth, and had received some treatment. The serological reactions during the period of observation were consistently negative. The heart sounds were always loud and pure.

The electrocardiograms obtained on admission showed (Fig. 1a) in the standard leads, the pattern of a left bundle branch block, without any other abnormalities. In the chest lead from position 2 (CF lead) there was, however, a distinct high take-off preceded by a wide and notched Q wave, proving the presence of a new anterior wall infarction. The chest lead in position 5 showed only the delay of the intrinsic wave over the left ventricle, which is characteristic of a left bundle branch block. An electrocardiogram obtained on June 11, 1948 (Fig. 1b) showed that the bundle branch block had disappeared. The QRS complexes were slurred without being widened and the voltage was low. There was, in addition, a high take-off of the RST segment in Lead 1, followed by a slight inversion of the T-wave. The R-wave was very low in position 2 and also in position 5 of the chest leads. In the latter lead an inverted T-wave is visible.

On June 9, 1948, a precordial pulsation was first noted above and inside the apical region. It impressed one as a small hemispheric bulge, a little more than 1 inch in diameter. A faint systolic and a diastolic gushing, high-pitched murmur were audible only over the pulsation. These murmurs per-

sisted until the patient was discharged in July, 1948. A chest plate on June 15th showed an aneurysmal bulge on the lower left cardiac border (Fig. 2). A stethogram (Fig. 3) was taken at the same time over the pulsation with a Cambridge unit. It revealed, in addition to a prolonged and occasionally split

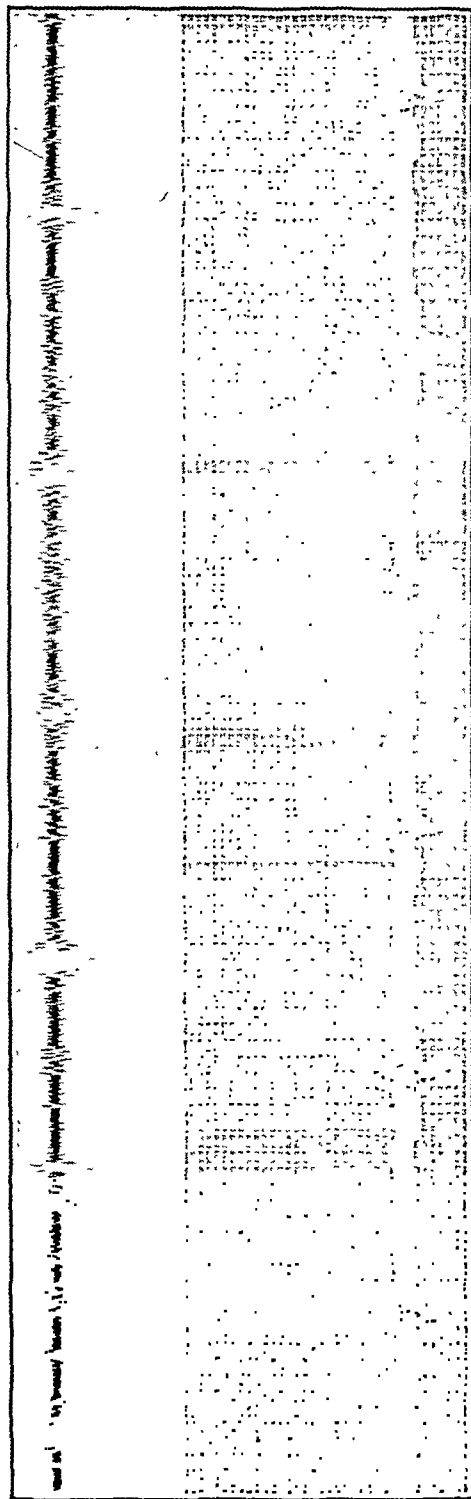


FIG. 3. Stethogram, taken over the pulsation in Case 1.



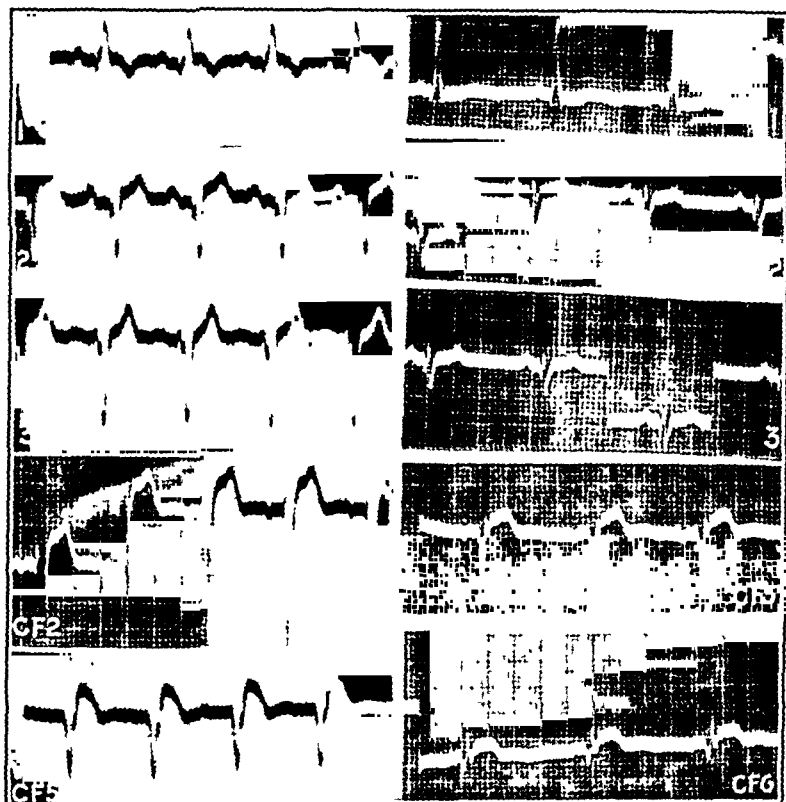


FIG. 4. CASE 2. Fig. 4a was obtained on the day after admission; Fig. 4b about 2 mos. later.



FIG. 5. Absence of pulsations in the kymogram of the left lower cardiac border

second sound, a faint systolic and a prolonged diastolic murmur. The systolic murmur in most of the cycles had an increased amplitude of vibrations toward the end of the systole and, at times, fused with the vibrations of the second sound. The diastolic murmur filled all diastole and in some cycles was louder toward the end of diastole. The auricular contraction was accompanied by an increased intensity of this murmur. Over the rest of the heart, only pure sounds were recorded.

The patient died suddenly at home in September, 1948.

CASE 2: M.J., a 64 year old man, had been hospitalized 2 years before his attack of myocardial infarction for hypertension (170/110) and congestive heart failure. At that time, the increase of blood pressure had already been known for 5 years. The gall bladder had been

removed in 1941 because of cholecystitis. The patient was readmitted on September 17, 1947, because of a continuous, sharp, constricting pain in the lower and mid-substernal regions, which radiated down both arms and up towards the neck. The pain began at midnight prior to admission and it waxed and waned until the patient entered the hospital. Associated symptoms were dyspnea, cold sweats, and nausea. The pressure fell to 128/96, the sedimentation rate rose to 85 mm.; the urea nitrogen rose temporarily to 37.5 mg. and the temperature to 101.1°. The white cell count was 14,250. There was no history of previous syphilis and the serological tests were repeatedly negative. The heart sounds were distant and pure. A protodiastolic gallop rhythm was heard during the first few days after admission.

The first electrocardiogram which was ob-

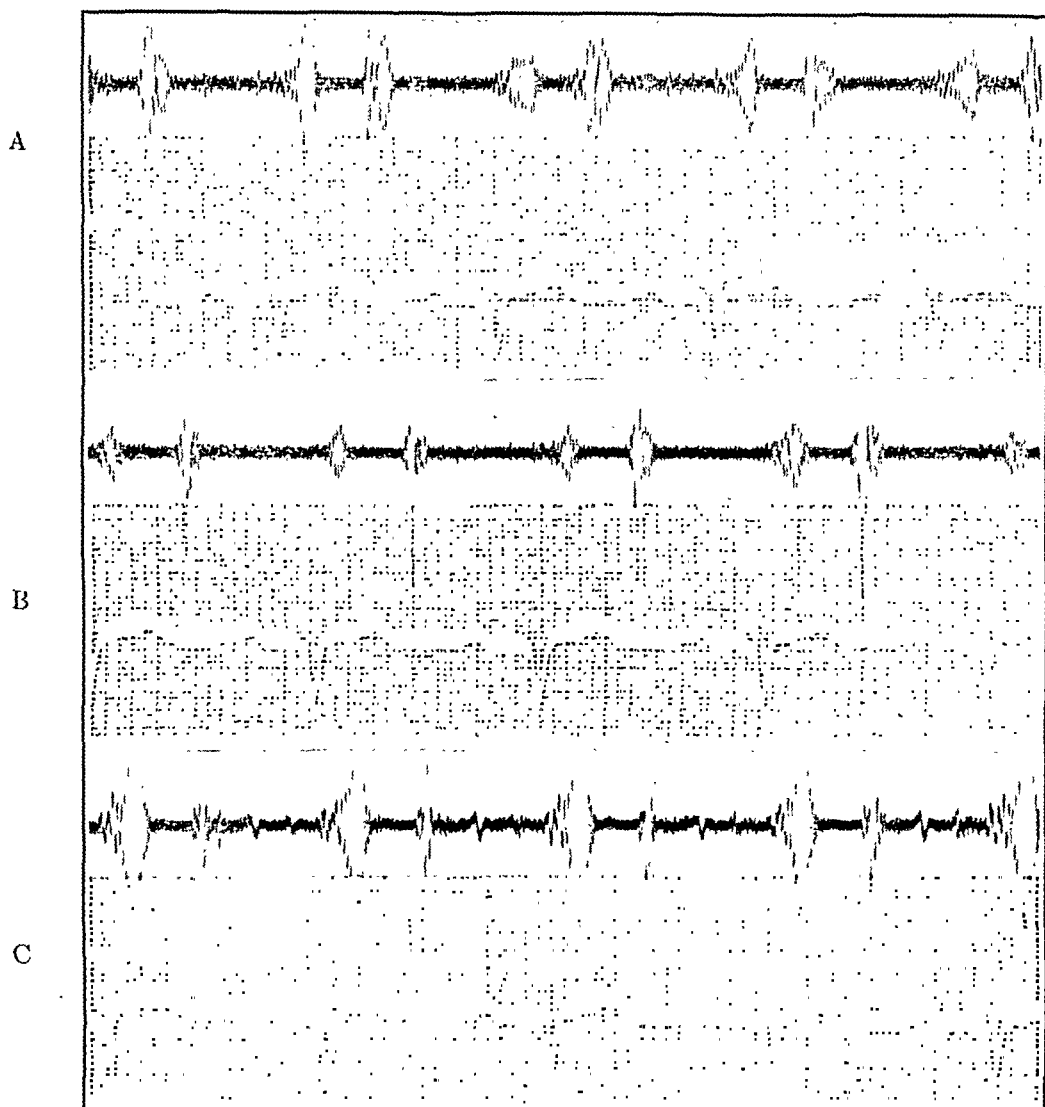


FIG. 6. Stethograms from the aorta (a), the pulmonary artery (b) and the apex (c).



mon in cardiac aneurysms. A kymographic study showed absence of pulsations on the lower left cardiac border (Fig. 5).

On October 1, abnormal pulsations over the same area as in Case 1 were observed for the first time; simultaneously, very loud systolic and diastolic murmurs were heard over the same region. During the following days the murmur became louder and reached its maximum intensity by mid-October.

A series of stethograms was taken on Octo-

The murmur merged with the first heart sound. Slightly mesial to the area of the pulsation, over the 4th intercostal space, just to the left of the sternum, the diastolic murmur was still present, although diminished in intensity (Fig. 7b). The splitting of the first sound was probably related to the intraventricular block.

On October 5, 1947, the patient suddenly developed severe pain in the right upper quadrant of the abdomen, with marked dyspnea,

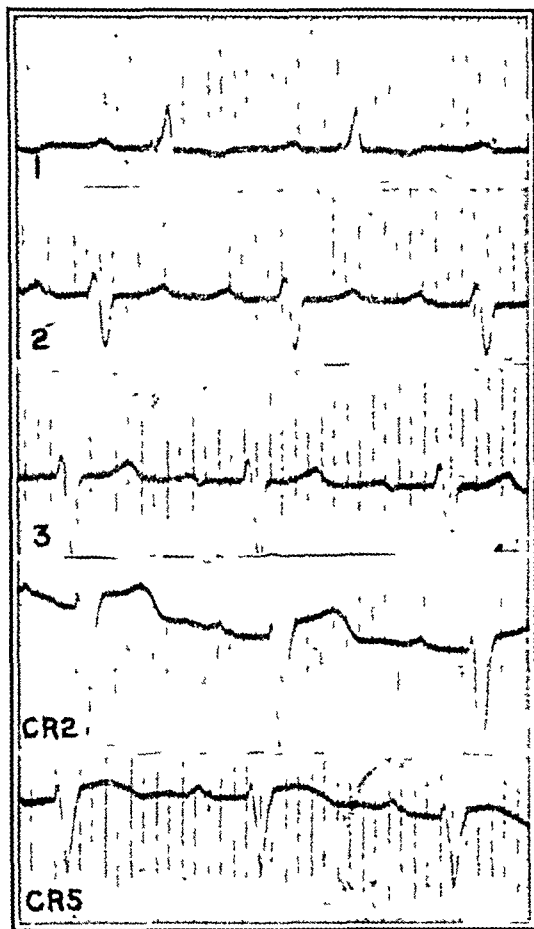


FIG. 9. Electrocardiogram of Case 3, showing in the chest leads an abnormally low R-wave and an elevated S-T and T.

ber 8, 1947. Over the aorta (Fig. 6a) the first sound is prolonged; the second sound is also prolonged and occasionally split. In some cycles there is a late systolic murmur, fusing with the vibrations of the second sound. Pure sounds were registered over the pulmonary artery (Fig. 6b) while a third sound and an auricular sound were recorded over the apex (Fig. 6c).

A loud diastolic murmur was registered over the pulsation of the aneurysm (Fig. 7a). It was continuous but increased in presystole.

orthopnea and sweating. The left leg became cold and there was severe pain. The blood pressure was 130/100. The patient was given oxygen, papaverine, aminophylline and morphine. Peripheral vein thrombosis and pulmonary embolism were diagnosed. The patient recovered from this episode and continued to improve. He was discharged on November 12, 1947. He died suddenly in January, 1948.

CASE 3: L.K., a 65 year old man, came under observation with a history of a myo-

cardial infarction which had occurred 2 years earlier. For 5 weeks prior to admission, the patient suffered from nocturnal dyspnea. The heart was enlarged to the left and its left lower border was clearly uneven on fluoroscopy. Fig. 8 shows the orthodiagram. A protodiastolic gallop rhythm was audible over the apical area. A systolic pulsation extended to the midclavicular line about 2 inches inside the apical area. Distinct systolic and diastolic murmurs were heard constantly over the pulsation for an observation period of more than 1 year. There was no history of and no findings due to a syphilitic infection. The blood pressure was 180/130 on the first examination and after compensation with digitalis it fell to 140/100.

The electrocardiogram showed a P-R interval of 0.24 second (Fig. 9). There was a left axis deviation with inverted T-waves in Lead 1. The CR-2 lead was normal, whereas in CR-5 the R-wave was abnormally low and the RST-segment was abnormally elevated. The stethogram showed normal sounds over the apex and the aorta and a long diastolic murmur, lasting throughout diastole over the pulsation of the aneurysm (Fig. 10). In this case as well the murmur was definitely accentuated toward the end of diastole.

**Discussion.** All 3 cases undoubtedly had sustained a myocardial infarction. This is proved by the typical clinical syndrome and by classical electrocardiograms, indicating the presence of a large transmural infarction of the anterolateral wall of the left ventricle. The absence of an R-wave in the chest leads over the lateral wall of the left ventricle cannot be interpreted otherwise.

The patients show a persistent elevation of the RST-segment in Lead I and particularly in the chest leads taken over the infarcted area<sup>7,12</sup>. This finding, which is common in transmural, "through and through" infarctions, is often misleading and makes the examining physician diagnose a fresh infarction. Since in patients with large transmural infarctions, aneurysms often develop, this electrocardiographic pattern is common in cardiac aneurysms of the anterolateral wall of the left ventricle.

All cases had roentgenologic findings

of a cardiac aneurysm and circumscribed bulging pulsations inside and above the apex area. In all cases systolic and diastolic murmurs were heard over this pulsation. The systolic murmur was somewhat rough and short. The diastolic one was high-pitched, gushing and soft; in all (or most) par-

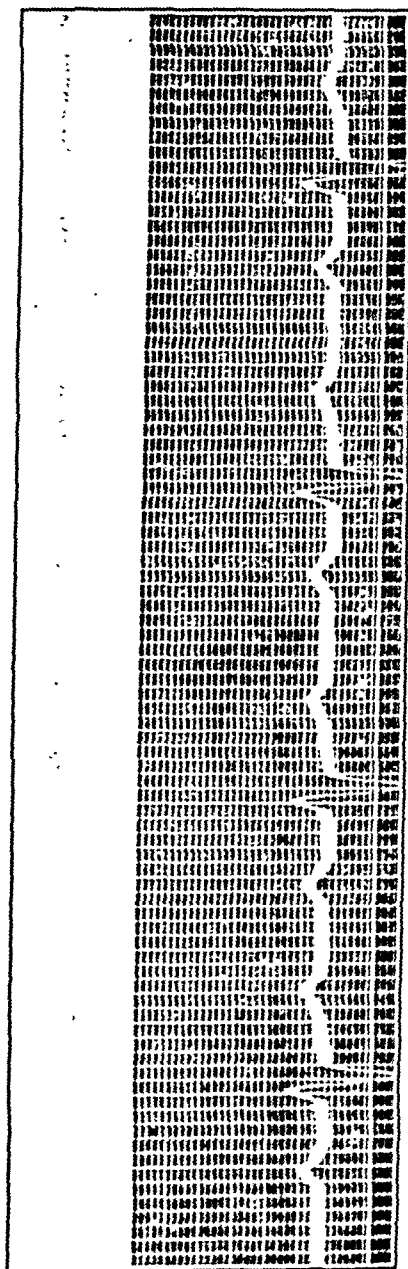


Fig. 10. Stethogram of Case 3.

ticulars it resembled the murmur heard in aortic regurgitation.

The last named lesion, insufficiency of the aortic valves, may easily be confused with a cardiac aneurysm because of the close resemblance of the murmurs. It is well known that in patients with insufficiency of the aortic valves particularly of rheumatic origin, the murmur is also heard on the left lower sternal border, very close to the site at which the murmur of the cardiac aneurysm usually is found. Actually, in 4 cases, one of us made the diagnosis of an aortic insufficiency despite the absence of its other signs, and yet autopsy revealed the presence of a cardiac aneurysm. This led us to pay particular attention to the auscultatory findings in this lesion. In the cases described in this paper, the absence of other signs of an aortic lesion, the presence of the murmur only over the left lower sternal border, and (as in Cases 1 and 2) its absence until some time after the occurrence of the myocardial infarction, made us rule out a lesion of the aortic valves due to a marked dilatation of the left ventricle. In one case of cardiac aneurysm described by Strandell, a diastolic murmur was heard, but autopsy revealed very rigid, calcified aortic valves.

For the differentiation between a diastolic murmur due to an insufficiency of the aortic valves and that of a cardiac aneurysm, the stethogram is of help. The vibrations due to an aortic regurgitation are very high-pitched and have their maximum intensity either immediately after the second sound or at the time of the rapid filling in early diastole; those recorded in our cases of aneurysm were present throughout diastole and experienced an increase in presystole.

In addition to the diastolic murmur of an aortic regurgitation two other phenomena must be differentiated. One is a gallop rhythm or a diastolic

third heart sound which often simulates a diastolic murmur. The roughness and evanescence of these extra sounds should make a distinction relatively easy, even without a stethogram. The second is a pericardial friction rub which may have two causes. One is due to dilatation of the heart *per se*. There is no doubt that even with a normal pericardium, dilatation of the left ventricle alone, particularly in children or in a person with a small chest, and even more often when the left lateral recumbent position is assumed, causes a fine, silky friction rub to appear. Presumably this is due to the friction between normal epi- and pericardium. This friction rub usually can be recognized by its auscultatory qualities and by its dependence on the phase of the respiration. In rare cases a permanent friction rub is heard in patients whose earlier pericarditis caused thickening and roughening of the pericardium without leading to an obliteration of the pericardial cavity. This phenomenon too causes vibrations which are recognized by auscultation alone.

To explain the origin of the aneurysmal murmur is difficult. It was believed that the passage of blood into the orifice of the aneurysm, which often is narrower than the largest diameter of the aneurysmal sac, causes the murmur<sup>3</sup>. Our findings, which show that the murmur is louder towards the end of diastole, speak somewhat against this conception unless one assumes that the auricular contraction forces blood with still greater force into the aneurysm and causes a turbulence of blood with formation of whirlpools. However, it must be assumed that the amount of residual blood in the left ventricle is greater than usual and that the aneurysmal sack is not empty at the beginning of diastole. If one assumes that the blood is forced into the aneurysmal sack during systole to cause the systolic pulsation and the systolic

murmur, and that the diastolic back-flow of blood into the left ventricle causes the diastolic murmur<sup>15</sup>, it is difficult to understand why the murmur should be louder at the end of diastole.

**Conclusions.** In 3 cases of cardiac aneurysm due to myocardial infarction a diastolic murmur has been registered

over the aneurysm with the stethogram. The murmur is loudest towards the end of diastole. The mechanism of origin of this murmur is discussed. These patients have a large transmural infarction which causes permanent displacement of the RST-segment otherwise seen only in the acute phase of a myocardial infarction.

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# CONGENITAL POLYCYSTIC DISEASE OF THE KIDNEY: REVIEW OF THE LITERATURE, AND DATA ON 207 CASES

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THE remarkable and not infrequent affliction of the kidneys known as polycystic disease has been recognized for several centuries but its pathogenesis has yet to be delineated. The numerous theories advanced as to its etiology may be conveniently described under the categories of metabolic, inflammatory, neoplastic, and developmental defects.

ETIOLOGY. Virchow<sup>34</sup> first suggested, on the basis of microscopic observations, that structural changes in the kidneys in this condition were due to deposition of salts in the renal tubules with resultant tubular obstruction followed by formation of cysts. Subsequently Virchow<sup>35</sup> suggested that papillitis or pyelitis in fetal life might cause tubular fibrosis, obstruction and cystic change. Ribbert<sup>27</sup> also suggested non-specific inflammatory changes during fetal life as the cause of the cystic changes but concluded that their effect was to prevent union of the uriniferous and collecting tubules. Numerous writers<sup>30,32</sup> have suggested fetal syphilis as the cause of the tubular obstruction.

Histologically many polycystic kidneys present the picture of vigorously growing tumors and only recently Staemmler<sup>31</sup> has applied the term "cystadenofibroma" to these changes. Brigidi and Severi<sup>5</sup>, however, were the first to suggest that polycystic disease of the kidney represents a true neoplastic process.

Since Kupffer<sup>15</sup> first demonstrated that the adult kidney is derived from two separate anlagen, there has been much speculation concerning how this peculiar process may influence the development of polycystic kidneys. Embryologically, the adult kidney is derived from the metanephros which forms the ureter and a series of 12 to 14 generations of buds from it which form the collecting tubules. The glomerulus, convoluted tubules and loop of Henle are formed from a condensation of mesenchyme overlying the budding metanephros and termed the "metanephric blastema"<sup>14</sup>. From his microscopic studies, Mutach<sup>21</sup> came to the conclusion that the cysts resulted from cessation of growth of the developing renal anlagen before union of the uriniferous and collecting tubules. Kampmeier<sup>13</sup>, and McKenna and Kampmeier<sup>18</sup>, as a result of careful reconstructions of serial sections of fetal kidneys and in 1 case of polycystic kidneys, were of the opinion that the fundamental defect in a polycystic kidney was failure of the 2nd to 4th generations of uriniferous tubules to atrophy. They found that these generations of uriniferous tubules joined with similar generations of collecting tubules but later (about the 3rd month of fetal life) separated and remained for about a month as cystic tubules. Kampmeier<sup>13</sup> was able to demonstrate as many as 40



of these cystic tubules in each kidney of normal fetuses 3 months of age. A few weeks later these tubules either atrophied or united with the 5th or later generations of collecting tubules. Polycystic kidneys, then, might represent a failure of atrophy of these particular generations of uriniferous tubules. More recently Norris and Herman<sup>23</sup>, on the basis of reconstructions of serial sections in 2 cases of infantile polycystic kidney and 2 cases of adult polycystic kidney disease, elaborated on Kampmeier's theory. They pointed out that many of the cysts undoubtedly are derived not only from uriniferous tubules but also from collecting tubules as noted by Forssman<sup>9</sup>. Also they found that there were anastomoses between the cysts in both prenatal and postnatal kidneys. They suggested that in polycystic disease of the kidney a much greater portion of the metanephros than normal is provisional and that during fetal life rapid growth and anastomosis of these collecting and uriniferous tubule cysts occur so that when these fail to atrophy, polycystic kidneys result. Moolten<sup>19</sup>, on the basis of histologic studies, has suggested that the primary defect is one of organizer action rather than one of cell competence. He regarded congenital polycystic disease of the kidney as a disseminated hamartosis similar to tuberous sclerosis and Lindau's disease.

In contrast to the multitude of theories, the amount of experimental work reported on which these theories have been based is small indeed. The foundation for these theories has been simple microscopic anatomy and, in some instances, reconstructions of serial sections. Petterson<sup>26</sup> and Tollens<sup>33</sup>, working independently, first investigated the results of renal tubular occlusion. Utilizing the rabbit, they cauterized or ligated the renal papillae and noted first a dilatation of the tubules followed shortly by atrophy and obliteration of

the epithelium and ending in a small contracted kidney which in no way resembled a polycystic kidney. These experiments, however, were not done on fetuses of rabbits, and it is possible that obstruction of the tubules of fetal animals would result in a different picture from that when the same procedure was carried out on the adult. Hepler<sup>11</sup>, and Hinman and Hepler<sup>12</sup> studied the development of hydronephrosis in dogs produced by ureteral ligation and noted that simultaneous partial occlusion of the renal artery hastened the development of the hydronephrotic process. If only one branch of the renal artery is occluded and the ureter to that kidney is ligated, then cystic dilatation develops in the infarcted portion of the kidney. Apparently renal ischemia in the presence of ureteral obstruction produces more rapid cystic change. The cyst, however, originates from the renal pelvis and does not involve tubules derived from the uriniferous tubules as do the cysts in cases of congenital cystic kidney.

Ritter and Baehr<sup>28</sup> injected the arterial tree with barium gelatin in 5 cases of congenital polycystic kidney, made roentgenograms, and noted a gross diminution in the number and size of the arterioles. This observation was confirmed by Schacht<sup>29</sup> who made histologic measurements of the ratio of the diameter of the arterioles to the width of their walls. He noted a decrease in this ratio in all polycystic kidneys that he examined: that is, a decrease in the diameter of the lumen and an increase in the width of the wall. Schacht suggested this change as the cause of hypertension in polycystic disease of the kidney, whereas Ritter and Baehr advance the hypothesis that arteriolesclerosis is the cause of polycystic disease itself.

Bagg<sup>1</sup> has been the only one to produce a polycystic kidney experimentally. This was done by unfiltered

Roentgen irradiation of the abdomen of one generation of mice, and careful examination of all their descendants. Polycystic kidney, renal aplasia, horseshoe kidney and other congenital anomalies appeared in a certain percentage of the members of the 3rd and 4th generations. He found that the tendency to congenital renal anomalies was inherited as a Mendelian recessive. No attempt has been made to relate irradiation to the development of congenital polycystic renal disease in human beings, although with the increasing use of radioactive isotopes such work would be of considerable interest.

Thus, with this one exception, the mechanism of which is unknown, it has been impossible to produce polycystic disease of the kidney in the laboratory. The most tenable theory at present is the one first suggested by Felix<sup>14</sup>, and later elaborated by Kampmeier<sup>13</sup>, that the uriniferous tubules of certain generations fail to atrophy or reunite with the collecting tubules resulting in the presence of a functioning glomerulus with no means of excreting the urine formed and the consequent development of multiple glomerular and tubular cysts. Undoubtedly the development of associated renal arteriosclerosis has a great influence on the progression of polycystic disease of the kidney.

**PRESENT STUDY.** The present report is based on study of 2 groups of cases; the first is composed of 207 cases of polycystic disease of the kidney seen at the Mayo Clinic from 1932 through 1947, and the second, of 46 cases of polycystic disease of the kidney in which complete necropsy data were obtained during the years 1920 through 1947. Of the patients in the first group 44 have been followed, usually by letter, until death, and 2 more have died and undergone necropsy at the clinic. The latter 2 have been included in the second group of 46 cases. Ninety-nine patients in the first group have been traced by letter or seen within the 12 months previous to August, 1948, and are still alive. We

have been unable to trace 62 patients. In all cases the diagnosis has been verified by: 1, intravenous or retrograde pyelograms; 2, by examination of the kidneys at the time of operation or, 3, at necropsy.

**DURATION OF LIFE.** The age of the patients when they first registered at the clinic is given in Table 1. The average age at death was 49.3 years when those infants dying before the age of 6 months of the infantile variety of polycystic disease of the kidney were excluded (Table 2). As this whole series extends over a relatively short period of time relative to life expectancy (only 17 years have elapsed since the first patient came to the clinic), it might seem that those patients who have died thus far had, in general, the more severe types of polycystic disease of the kidney, and the average life expectancy should be corrected upward.

TABLE 1. AGE AT TIME OF DIAGNOSIS AT CLINIC AND SEX DISTRIBUTION

| Age<br>years and sex | Cases | %   |
|----------------------|-------|-----|
| 0-9                  | 6     | 3   |
| 10-19                | 2     | 1   |
| 20-29                | 18    | 9   |
| 30-39                | 71    | 34  |
| 40-49                | 56    | 27  |
| 50-59                | 41    | 20  |
| 60 or more           | 13    | 6   |
| Total                | 207   | 100 |
| Sex                  |       |     |
| Males                | 94    | 45  |
| Females              | 113   | 55  |
| Total                | 207   | 100 |

TABLE 2. AVERAGE DURATION OF LIFE (EXCLUDING INFANTILE VARIETY)

|  | Traced<br>patients | Average<br>age, years |
|--|--------------------|-----------------------|
| Patients first seen before 1943,<br>still living                                   | 55                 | 51.5                  |
| Patients who have died (ex-<br>cluding the infantile type of<br>polycystic kidney) | 85                 | 49.3                  |
| Duration of life after onset<br>of symptoms  | 43                 | 9.3°                  |
| Duration of life after onset<br>of azotemia  | 17                 | 2.2°                  |

° Duration in years after onset of symptoms.

Hence, the average age of all patients who were traced and found to be still alive 5 years or more after the diagnosis was made was determined. This was 51.5 years. Obviously the life expectancy of these patients is an indeterminate number of years greater than 51.5, yet they must be included with the previous group to form an accurate appraisal of the true life expectancy of a patient with polycystic disease of the kidney. So, although the life expectancy of the average patient with polycystic disease of the kidney cannot be determined exactly from these data, it must be somewhat more than 50 years. The necropsy data also suggest that many patients with this disease may live a normal life span, for it may be seen that 22% of the patients lived to be 60 years of age or older. Also, we are in correspondence with 2 patients, 84 years of age, who have polycystic disease of the kidney which was first diagnosed 16 and 10 years ago respectively and who are at this time in good health.

We were able to date the onset of symptoms of 43 patients with a reasonable degree of accuracy and follow them until death. The time interval averaged 9.3 years. The 17 patients for whom we could more or less accurately determine the onset of azotemia (as indicated by a concentration of urea in the blood of more than 40 mg. per 100 cc.) lived on the average of 2.2 years, and 1 patient lived 5½ years. This strikes a somewhat more optimistic note than some figures in the literature. Nolan<sup>22</sup> said, for example, that 50% of patients who have polycystic kidneys are dead 4 years after the diagnosis is made. Oppenheimer<sup>24</sup>, however, has reported on a series of 60 patients whose average age at death was 50 years, and whose average age at the onset of symptoms was 41.5 years. Our data suggest that the evaluation of any therapeutic procedure must be tem-

pered by the fact that present conservative medical measures may result in a life expectancy after the onset of symptoms of almost 10 years for the average patient. In 199 of the 207 cases studied no specific treatment was suggested. In 8 cases, puncture of the cysts, the Rovsing procedure, was performed. This was done primarily for the relief of intractable pain.

**CLINICAL DATA.** The sex distribution in our 207 cases was essentially the same as that reported by Braasch and Schacht<sup>4</sup> in 1932, which showed no predilection for either sex. In about a third of the patients we were able to elicit a family history of polycystic kidneys and, in a fourth more, a questionable familial history of the disease; for example, the mother and two brothers of 1 patient died of kidney disease (Table 3). The difficulty of examining

TABLE 3. FAMILY HISTORY OF POLYCYSTIC KIDNEY

| Family history        | Cases | %   |
|-----------------------|-------|-----|
| Positive and definite | 72    | 34  |
| Questionable          | 55    | 27  |
| Negative              | 80    | 39  |
| Total                 | 207   | 100 |

all relatives of patients living at a distance from the clinic prevented accurate tracing of a sufficient number of families to establish the manner of inheritance of this condition. Bell<sup>2</sup> has expressed the opinion that polycystic kidneys are inherited as a Mendelian dominant although enough complete genealogies have not been made to establish this conclusively. We have referred previously to the observation of Baggs<sup>1</sup> that the descendants of irradiated mice inherited polycystic kidneys as a recessive tendency. Numerous instances of polycystic kidneys in families have been noted: 17 of 40 members of one family<sup>5</sup>, 9 of 27 members of 4 generations in another<sup>10</sup>, 5 children of the same mother<sup>7</sup>, and 6 persons in 2 generations of the same

family<sup>25</sup> have had polycystic kidneys.

The main presenting complaints of our 207 patients at the time the diagnosis of polycystic kidneys was made are given in Table 4. The pain for

TABLE 4. CLINICAL DATA

| Presenting complaint or findings  | Cases        | %   |
|---|--------------|-----|
| <i>Presenting complaint</i>   |              |     |
| Lumbar or abdominal pain  | 58           | 28  |
| Presence of abdominal mass  | 42           | 20  |
| Elevated blood pressure   | 35           | 17  |
| Frequency, urgency or burning on urination                                      | 36           | 17  |
| Painless hematuria  | 26           | 13  |
| Hematuria and renal pain  | 21           | 10  |
| Kidney failure (edema, uremia and so forth)                                     | 2            | 1   |
| None related to kidneys   | 39           | 19  |
| <i>Findings on physical examination</i>   |              |     |
| Elevated blood pressure (more than 140 mm. of Hg. systolic or 90 mm. diastolic) | 146 (of 200) | 73° |
| Palpable, enlarged kidney or kidneys  | 150 (of 207) | 72† |

\* % of 200 cases in which blood pressure was recorded.

† % of 207 cases.

which about two-fifths of these patients came to the clinic had no definite pattern. It was located in the lumbar region or upper or lower part of the abdomen. It was usually nagging and dull, although attacks of colic were not uncommon. Colicky pain sometimes was associated with hematuria as a result of the ureteral spasm while blood clots were passed and in some cases it was an indication of associated renal calculi.

Of our 207 patients 20% came to the clinic because of the presence of an abdominal mass, discovered either by themselves or by their physicians. One-sixth of the patients came to the clinic because of the previous finding of high blood pressure. This further emphasized the frequent occurrence of hypertension in cases of polycystic disease of the kidneys, a point first noted by Braasch<sup>3</sup> in 1916. The

rather large number (17%) of patients whose presenting complaints were of urinary frequency, urgency, burning or incontinence, emphasizes the frequency of renal and vesical infection in cases of polycystic kidneys. Sulfonamides, penicillin and streptomycin are of invaluable aid in the treatment of these common complications of polycystic disease of the kidney. The high incidence of painless hematuria in patients with this disease has been emphasized but is not entirely substantiated by our series since it was noted by less than 12% of our patients<sup>16,17</sup>.

A blood pressure consistently higher than 140 mm. of mercury systolic or 90 mm. diastolic, in 73% of our cases is in accord with Braasch and Schacht's<sup>4</sup> observations. The fact that almost 72% of the patients on admission had palpable, enlarged kidneys (one or both) re-emphasizes the importance of this feature in the diagnosis of polycystic disease of the kidney.

The ocular fundi were examined in 105 of our 207 cases. In 71.5% changes typical of hypertension were noted, and, although an attempt was made to correlate these findings with the severity of the hypertension and the extent of renal failure (Table 5), no clear-cut evidence was obtained.

TABLE 5. CHANGES IN OCULAR FUNDI IN 105 CASES

| Blood pressure   | Ocular fundi<br>(changes, grades 1 to 4°) |    |    |   |   |
|--|---|----|----|---|---|
|  | Normal                                    | 1  | 2  | 3 | 4 |
| Normal (less than 140/90)  | 9   | 2  | 2  |   |   |
| Between 140/90 and 180/110                                       | 14  | 13 | 4  |   |   |
| More than 180/110  | 2   | 12 | 8  | 1 |   |
| Elevated blood pressure and elevated concentration of blood urea | 5   | 21 | 9  | 1 | 2 |
| Total  | 30  | 48 | 23 | 2 | 2 |

\* Based on classification of Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease With Hypertension, and Associated Retinal Lesions. *Medicine*, 18, 317, 1939.

The intravenous pyelogram usually presented a typical appearance. The calices were elongated and there was some blunting and irregularity of outline.

Albuminuria, pyuria, and somewhat less frequently, hematuria, were noted in most of the patients with polycystic disease of the kidney. The high incidence of pyuria (Table 6) suggests

TABLE 6. LABORATORY STUDIES

|  | Cases      | %  |
|--|------------|----|
| Albuminuria  |            |    |
| None   | 46         | 22 |
| Grade 1 to 2+  | 143        | 69 |
| Grade 3 to 4+  | 18         | 9  |
| Hematuria  |            |    |
| None   | 156        | 75 |
| Grade 1 to 2+  | 33         | 16 |
| Grade 3 to 4+  | 18         | 9  |
| Pyuria   |            |    |
| None   | 64         | 31 |
| Grade 1 to 2+  | 121        | 58 |
| Grade 3 to 4+  | 22         | 11 |
| Elevated value for blood urea (more than 40 mg. per 100 cc.) | — (of 198) | 36 |
| Associated nephrolithiasis                                   | 29         | 14 |

again the frequency of infections of the urinary tract in these patients. Nitrogen retention as indicated by elevated levels of blood urea in more than a third of the patients on the occasion when their polycystic kidneys were first noted, indicates how long they are able to get along without symptoms. The 14% incidence of nephrolithiasis is not as high as some authors have reported (Oppenheimer<sup>21</sup> noted 23.7% in a series of 60 cases), but appears to us to be significant. Hyperparathyroidism secondary to renal failure of long duration may be considered as a possible cause of the calculi, but of the 29 patients who had renal calculi, only 11 had an elevated concentration of urea in the blood. This is 35% or essentially the same incidence found in the group without stones. Stagnation of urine, infection and subsequent formation of

calculi, therefore, seem more likely to be the pathogenesis.

The electrocardiograms in these cases showed no changes other than those which might be expected as a result of hypertension of some duration. Left axis deviation was the most common finding and was noted in 71% of 21 cases in which electrocardiograms were made. Changes in T waves were not infrequent, as inverted T waves were present in Lead 1 in 29%, in Lead 2 in 19% and in Lead 3 in 24% of cases. Only 1 instance of right axis deviation was noted.

NECROPSY DATA. Data derived from 46 necropsies on patients who had polycystic disease of the kidney are given in Tables 7 to 9. Several features may be noted concerning the age at death: 1, the high incidence of children less than 1 year of age, and, 2, the low incidence of patients from 1 to 40 years of age. The first point has been mentioned by Bell who regarded polycystic

TABLE 7. NECROPSY DATA IN 46 CASES CONCERNING AGE AT DEATH, SEX DISTRIBUTION, KIDNEYS INVOLVED AND SIZE AND WEIGHT OF HEART

| Age (years) distribution:                          | Cases    | %   |
|--|----------|-----|
| 0-1  | 9        | 20  |
| 1-9  | 0        | 0   |
| 10-19  | 2        | 4   |
| 20-29  | 1        | 2   |
| 30-39  | 2        | 4   |
| 40-49  | 11       | 24  |
| 50-59  | 11       | 24  |
| 60-69  | 5        | 11  |
| 70 or more   | 5        | 11  |
| Total cases  | 46       | 100 |
| Sex distribution: Males                            | 34       | 74  |
| Females  | 12       | 26  |
| Kidneys involved: One                              | 6        | 13  |
| Both   | 40       | 87  |
| Heart, size and weight: Hypertrophy of heart noted | 24       | 52  |
| Average weight of these hypertrophied hearts       | 512 gm.* |     |

\* 2 cases of valvular heart disease excluded.

TABLE 8. CAUSE OF DEATH IN 46 CASES

|   | Cases | %  |
|---|-------|----|
| Kidney failure with uremia                  | 9*    | 20 |
| Myocardial infarction                       | 6     | 13 |
| Cerebral hemorrhage                         | 4†    | 9  |
| Cardiac failure                             | 3‡    | 7  |
| Multiple congenital anomalies               | 3     | 7  |
| Prematurity                                 | 3     | 7  |
| Generalized peritonitis                     | 6     | 13 |
| Postoperative, 4                            |       |    |
| Postirradiation, 1                          |       |    |
| After perforated appendix, 1                |       |    |
| Paralytic ileus (postoperative)             | 1     |    |
| Lobar pneumonia                             | 1     |    |
| Bronchopneumonia                            | 2     |    |
| Pulmonary edema                             | 1     |    |
| Suppurative bronchitis                      | 1     |    |
| Lupus erythematosus                         | 1     |    |
| Spongiblastoma multiforme                   | 1     |    |
| Pulmonary tuberculosis                      | 1     |    |
| Hemorrhage from ruptured esophageal varices | 1     |    |
| Cerebral thrombosis                         | 1     |    |
| Basilar meningitis                          | 1     |    |

\* One case of chronic glomerulonephritis included.

† Case of one infant with cerebral hemorrhage as a result of birth trauma included.

‡ One case of rheumatic endocarditis included.

TABLE 9. ASSOCIATED CONGENITAL ANOMALIES ENCOUNTERED IN 46 CASES OF POLYCYSTIC DISEASE OF THE KIDNEY AT NECROPSY

| Associated congenital anomalies                       | Cases | %  |
|---|-------|----|
| Polycystic liver                                      | 15    | 33 |
| Polycystic pancreas                                   | 4     | 9  |
| Polycystic spleen                                     | 1     | 2  |
| Cardiac defects                                       | 4     | 9  |
| Defects of nervous system                             | 2     | 4  |
| Genito-urinary defects (other than polycystic kidney) | 6     | 13 |
| Defects of gastro-intestinal tract                    | 3     | 7  |
| Defects of the musculoskeletal system                 | 2     | 4  |
| Total   | 37    | 81 |

disease of the kidney in children as a distinct sub-group. In cases of infantile polycystic kidney disease there is also an unusually high incidence of other congenital anomalies. In 7 of the 9 cases in our series, multiple congenital

anomalies were present. It would appear that some major defect in embryonic life affecting most of the organs of the body produces these cases of infantile polycystic kidney disease. The low incidence of death from polycystic disease of the kidney in the age group from 1 to 40 years suggests that some process of aging as well as polycystic disease of the kidney *per se* may be operative in causing these deaths. Hinman's data<sup>12</sup> demonstrating the rapidity with which cystic damage proceeds in a kidney with impaired blood supply, together with the data of Schacht<sup>29</sup>, and of Ritter and Baehr<sup>28</sup> on arteriolosclerosis in polycystic kidneys, is suggestive that polycystic kidneys may experience no serious functional difficulty until impaired blood supply weakens the parenchyma and supporting tissue to permit rapid development of the cysts.

The finding of unilateral polycystic disease of the kidney in 13% of the cases studied at necropsy is somewhat unusual, although such cases have been reported. Fevre and Tran Van Hoa<sup>8</sup> found 11 cases (68%) of unilateral disease in 16 cases of polycystic kidneys among children. Bell<sup>2</sup> reported 8 cases of unilateral involvement in a series of 48. Lejars<sup>16</sup> noted 3 cases of unilateral polycystic kidney in his series of 62 cases. Oppenheimer<sup>24</sup> and Lowsley and Curtis<sup>17</sup> reported that in series of 60 and 53 cases, respectively, they found no cases of unilateral polycystic kidney. The impossibility of verifying the diagnosis of polycystic disease affecting only one kidney without necropsy data vitiates much of such data, however.

The causes of death (Table 8) in this series show some interesting features. Slightly under a fifth of the patients died as a result of renal failure. Even if deaths from the effects of hypertension accompanying polycystic kidney disease (cardiac failure, myocardial

infarction, and cerebral hemorrhage) are included, the incidence is still less than 50%. The high postoperative mortality rate (5 deaths may be noted in Table 8) might suggest, as was once felt, that patients with polycystic renal disease are poor surgical risks. The fact that all but one of these deaths occurred before the days of sulfonamides and penicillin indicates that this is no longer true.

The incidence of associated congenital anomalies is shown in Table 9, and reaffirms their reported frequency. Polycystic disease of the liver in particular, is associated with polycystic disease of the kidney. Moschcowitz<sup>20</sup> reported an incidence of 19% and Oppenheimer<sup>24</sup> 28.5% of cystic involvement of the liver in their series of cases of polycystic disease of the kidney. There were no symptoms in our entire clinical group of 207 cases suggestive of polycystic disease of the liver although Waterson and Morgan<sup>26</sup> reported a remarkable instance of jaundice in a patient known to have polycystic disease of the kidney. The jaundice in this case was relieved by evacuation of 284 cc. of fluid from cysts in the liver.

Cardiac hypertrophy was noted in 52.3% of our 46 cases in which necropsy was performed; the average weight of the hearts, exclusive of those with associated valvular heart disease, was 512 gm. The largest weighed 712 gm. This is somewhat at variance with the experience of Bell<sup>2</sup> who reported minimal, if any, cardiac hypertrophy in this disease.

**Summary and Conclusions.** From our study, we may conclude that the typical patient with congenital poly-

cystic disease of the kidneys will have a family history of renal disease and may expect symptoms to appear during the fourth or fifth decade of life. These symptoms in about two-fifths of the cases will consist of dragging abdominal or lumbar pain accompanied by some abdominal enlargement. A history of recurrent infections of the urinary tract and possibly renal colic may be elicited. On examination one or both kidneys may be palpated as irregular, hard masses. The blood pressure will probably be found to be moderately elevated with minimal to moderate hypertensive changes in the ocular fundi. Laboratory examinations may reveal albuminuria and pyuria of varying degrees. The intravenous pyelogram will show elongated calices with some blunting and irregularity of outline. Such a patient ordinarily will have a life expectancy of approximately 10 years after the onset of symptoms and has a fair chance for a normal life span. A poor prognosis is indicated by increase in the size of the kidneys, increase in severity of symptoms, progression in associated hypertensive vascular disease or advancing impairment of renal function.

Clinical data are presented on 207 proved cases of congenital polycystic disease of the kidney and certain common features emphasized. A more optimistic attitude toward such patients is suggested by an average age at death of almost 50 years. Necropsy data in 46 cases of polycystic disease of the kidney reveal a frequency of unilateral polycystic disease, the common occurrence of associated congenital malformations, and differential features between infantile and adult polycystic disease of the kidney.

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## DIABETIC NEPHROPATHY

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FOCAL hyalinization in the intercapillary connective tissue of the kidney in diabetes mellitus was described in 1936 by Kimmelstiel and Wilson<sup>10</sup>. They termed this newly recognized lesion intercapillary glomerulosclerosis and related it to a clinical syndrome. Characterizing the latter in addition to diabetes mellitus was proteinuria, widespread edema, hypertension and eventual renal failure.

Murakami<sup>12</sup>, shortly after the original publication, also recognized the lesion in a diabetic. In 1938 Anson<sup>2</sup> concluded that the histologic findings of intercapillary glomerulosclerosis may be anticipated if the patient has hypertension and mild diabetes. Derow, Altschule and Schlesinger<sup>4</sup> in 1939 published several case reports of intercapillary glomerulosclerosis and discussed the specificity of the lesion. Widespread vascular degeneration was proposed as a factor in the pathogenesis by Newburger and Peters<sup>13</sup> in 1939. Porter and Walker<sup>15</sup> presented a discussion of the clinical syndrome, as did Siegal and Allen<sup>16</sup>. Herbut<sup>7</sup> found 11 characteristic examples of intercapillary glomerulosclerosis in a large number of autopsies. An excellent study was conducted by Allen<sup>1</sup>. After finding the lesion in 33% of diabetic patients of 40 years or more, he concluded that a new and more reliable criterion was available for the post-mortem diagnosis of diabetes mellitus.

The clinical syndrome is not recognized as frequently as is the kidney lesion. This suggests that the glomerular changes do not always result in

a nephrotic hypertensive patient. In this regard, Laipply, Eitzen and Dutra<sup>11</sup> tried to correlate the pathologic and clinical components of the syndrome, and found no constant relationship.

At present most authors<sup>1,6,7,11,17,19</sup> agree that the renal lesion is rare in people who do not have diabetes. Siegal and Allen<sup>16</sup> found the lesion in only 1 case during the examination of 200 non-diabetic kidneys. By contrast, Horn and Smetana<sup>8</sup> contend that early examples of focal hyalinization may be found in many non-diabetics who have other kidney pathology. Their conclusion is based upon finding the lesion in nephrosclerosis, generalized arteriosclerosis and glomerulonephritis. Consolidating much of the information available in the literature, Kimmelstiel and Porter<sup>5</sup> recently presented an outstanding review of the diabetic syndrome.

The purpose of this report is to assist in achieving a necessary reorientation. The validity of unconfirmed or partially confirmed presumptions must be determined. Whether or not this lesion is pathognomonic of diabetes has been questioned. A high incidence in the diabetic alone would be of inestimable diagnostic value to the pathologist. Present histologic methods of diagnosis of diabetes are difficult to interpret accurately. Recognition of focal hyalinization, by contrast, presents little difficulty with routine stains.

The clinical aspects of the condition also need clarification. The end stages of the disease have received much

attention in reports stressing the features originally described by Kimmelstiel and Wilson. Uncertainty still exists concerning the clinical recognition of the early pathologic lesions.

Questions of morphology remain. Laipply, Eitzen and Dutra<sup>11</sup> have expanded the criteria set by Kimmelstiel and Wilson<sup>10</sup>. The former describe fibrosis of the glomerulus as an early stage of intercapillary glomerulosclerosis. Their statistics show a rise over all former reports, due to this interpretation. The question, however, is open to further investigation and will be discussed below.

The blood pressure reading selected was taken to represent the patient in his most basal condition. Instances existed where complications obscured the true readings. Therefore, hypertension in most cases was confirmed by the size of the heart at necropsy. Separation of the normal from the hypertensive group was accomplished by using systolic pressure of 150 mm. and diastolic pressure of 90 mm. as the point of division.

The clinical charts were examined for data as to sex, duration of the disease, proteinuria, azotemia, and the nephrotic syndrome.

To correlate the lesion with the duration of diabetes the patients were divided into groups of 5 year intervals up to 15 years' duration. All those above the latter figure were grouped together. The information in many cases was

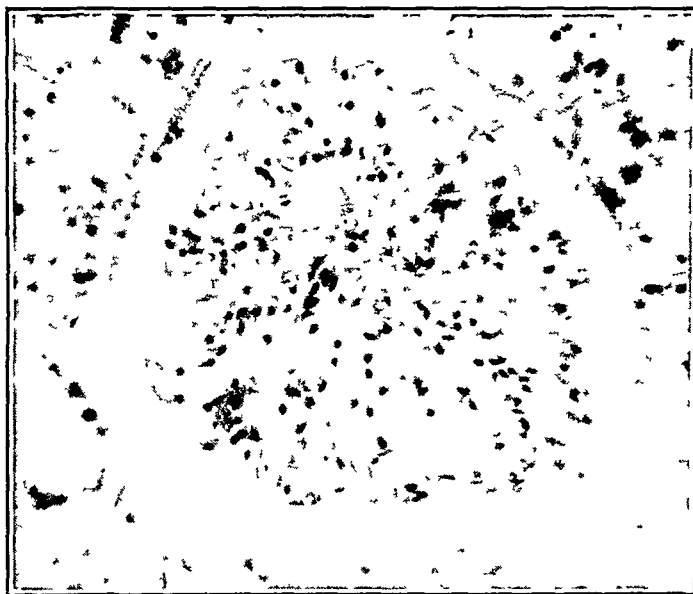


FIG. 1. Diabetic glomerulus demonstrating diffuse involvement of walls of the capillaries. Classified as "minimal" intercapillary glomerulosclerosis.

**Material and Method.** Fifty consecutive autopsies of diabetic men and women were reviewed. Sections of kidneys were studied with a modified Masson trichrome stain accentuating connective tissue. The lesion when found was reported as minimal, moderate or severe. The criteria for this classification are discussed in our consideration of the morphology.

Grading the severity of diabetes was done arbitrarily on the basis of insulin requirements daily as determined from the clinical histories. Diabetes was considered mild if up to 15 units of insulin were required; moderate if 16 to 40 units; and severe if 40 or more units were required daily.

questionable, these were called "unknown duration" and eliminated from consideration. For further elucidation the average duration of diabetes was analyzed and graphed.

Patients were regarded as having had moderate nitrogen retention or azotemia when the blood urea nitrogen was in the range of 40 to 60 mg. per 100 cc. Arbitrarily all above the latter figure were called uremic. In many cases renal and pre-renal azotemia due to heart failure could not be differentiated.

The nephrotic syndrome includes patients with plasma proteins below 5.5 gm. per 100 cc., proteinuria of long standing, generalized edema and hypercholesterolemia.

When the cholesterol was not reported but other criteria were typical we did not hesitate to include the case in our group.

In demonstrating the relationship of intercapillary glomerulosclerosis and arteriosclerosis, we used gangrene as indicative of advanced peripheral vascular disease. In all these cases amputation had been performed or a gangrenous lesion was found at autopsy. While many extrinsic factors exist in the etiology of gangrene in diabetes, advancing arterial and arteriolar sclerosis is the basic defect. In an attempt to relate the two pathologic processes others have compared the degree of renal vessel sclerosis with the stage of development of intercapillary glomerulosclerosis. We have approached the problem (comparing peripheral vascular pathology with

cumferential laminated structures containing a few very small vacuoles. This hyaline does not react positively to stains that show amyloid. It is acidophilic with hematoxylin and eosin and stains green with modified Masson trichrome stain. Around the spherical lesion there are flattened cells in concentric layers. The center of the lesion usually contains no cells, but on occasion the remnants of a pyknotic nucleus may be found. The size varies from that of a small number of cells to involvement of an entire glomerulus. In the late stages the latter is often



FIG. 2. A typical spherical hyaline body in the glomerulus of a diabetic. Classified as "moderate" intercapillary glomerulosclerosis.

advancing diabetic nephropathy) to reach a conclusion fortified by additional facts.

The controls used in the estimation of the histologic lesion were 50 non-diabetics of a corresponding age group with kidney involvement such as benign nephrosclerosis, chronic glomerulonephritis, and chronic pyelonephritis.

**MORPHOLOGY OF THE LESION.** The typical lesion consists of spherical, dense hyalinized material between the glomerular tufts which appear homogeneous under low power. Under higher magnification one can see cir-

shrunk. Thickening of the afferent arteriole is often seen.

All degrees of involvement may be found in one glomerulus or it is possible to find only one lesion in several sections of the kidney. In sections showing the lesions many of the glomeruli show evidence of fibrosis. The lesion may not be apparent in the typical spherical form, but focal or diffuse fibrosis of the connective tissue of the glomerulus leads to more intense study and eventually the hyaline oval

mass will be found. For this reason we recognize glomerular fibrosis as a lesser involvement which may progress to the spherical lesion. Others<sup>11</sup> have reported this stage of intercapillary glomerulosclerosis in 24% of the diabetic patients with the lesion. Our figure is confirmatory, placing the incidence slightly higher. The validity of the association of lesions can often be demonstrated by searching through many sections of the same kidney. In addition to the glomerular fibrosis, an occasional hya-

should not be confusing. Other findings in this disease include focal necrosis in many of the glomeruli which is missing in the diabetic kidney. Finding the characteristic "wire loop" of lupus erythematosus makes separation definite.

In our study fibrosis of the glomerulus was classified as the minimal lesion of intercapillary glomerulosclerosis. Glomeruli containing occasional spherical hyalinized lesions were listed as moderately involved. The advanced

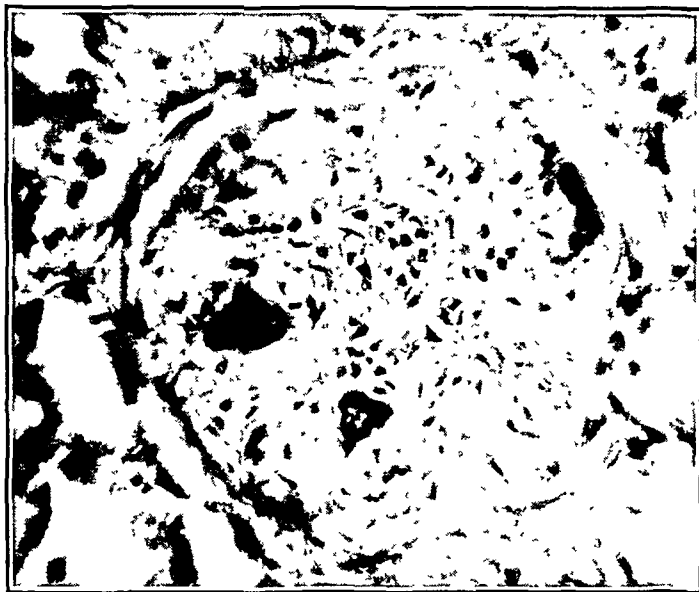


FIG. 3. A classical lesion of the advanced clinical syndrome in diabetes. There is complete involvement of the glomerulus by the disease process. Classified as "advanced" intercapillary glomerulosclerosis.

linized glomerular tuft can be seen. It is possible that benign nephrosclerosis, chronic pyelonephritis, or chronic glomerulonephritis will simulate this closely. These lesions have variations in fibrosis from one glomerulus to the next in addition to other changes which do not occur in intercapillary glomerulosclerosis. The diffuse lesion, however, is not always readily identified as specific for diabetes.

Glomerular fibrosis described in disseminated lupus erythematosus

lesion was considered present when hyalinization existed in all glomeruli.

Whether or not diabetic glomerulosclerosis is "intercapillary" has raised conjecture. This descriptive term was given by Kimmelstiel and Wilson because they believed the lesion developed from hyalinization of the connective tissues between the capillaries. Allen<sup>1</sup> questioned this hypothesis. After studying the nature of hyalinization and observing staining qualities, he concluded that the hyaline is deposited in the wall of the capillary loop, and

a more accurate description would be "intramural" glomerulosclerosis. Serial sections of the lesion have affirmed this conclusion. The three dimensional description of the hyalinization would present the spherical lesion as a focal mass of hyalinization through which the capillary courses. Hyalinization and thickening extend from the capillary system in the glomerulus to the afferent arteriole where the intramural hyalinization is easily recognized<sup>3</sup>. Unfortunately the term "intercapillary" seems too deeply entrenched in the literature to be replaced. With misgivings, but for uniformity, we shall retain the original term.

**INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS.** In our series, glomerular disease was discovered in 82% of the diabetics (Table 1). Previous

claimed<sup>8</sup>. The control group studied affirms previous conclusions that moderate or advanced intercapillary glomerulosclerosis is rare in the absence of diabetes<sup>1,6,7,11,17,19</sup>. Our figure of 2% incidence of moderate or advanced lesions in non-diabetics is based on finding the typical lesion in a 63 year old female who died on admission. Since blood sugar and urinary sugar determinations were not made, the possibility of diabetes cannot be excluded. This case may be similar to other reported non-diabetics who present evidence of the hyaline change of intercapillary glomerulosclerosis. The minimal lesion was indistinguishable from many lesions found in non-diabetics. Hence no accurate estimate of its specificity can be made.

Latent diabetes may account for the

TABLE 1. INCIDENCE OF INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETIC AND NON-DIABETIC NEPHROPATHY.

|              | Total Cases | Present  | Absent   | Minimal  | Moderate | Advanced |
|--------------|-------------|----------|----------|----------|----------|----------|
| Diabetic     | 50          | 41 (82%) | 9 (18%)  | 17 (34%) | 20 (40%) | 4 (8%)   |
| Non-Diabetic | 50          | 8 (16%)  | 42 (84%) | 7 (14%)  | 1 (2%)   |          |

TABLE 2. REPORTED INCIDENCES OF INTERCAPILLARY GLOMERULOSCLEROSIS IN DIABETICS.

| Author                    | Year | Percentage |
|---------------------------|------|------------|
| Siegal and Allen          | 1941 | 33.3%      |
| Allen                     | 1941 | 33. %      |
| Horn and Smetana          | 1942 | 22.9%      |
| Bell                      | 1942 | 20.5%      |
| Spuhler                   | 1943 | 50. %      |
| Laipply, Eitzen and Dutra | 1944 | 63.5%      |
| Goodof                    | 1945 | 44. %      |

studies place the incidence between 20.5 and 63.5%. Authors and their figures are given (Table 2). Increasing recognition of the stage of fibrosis by many authors explains the increase in incidence in recent studies.

By including in the controls non-diabetic nephrosclerotics and glomerulonephritics, we were able to discover whether the lesion of spherical hyaline change was present in other pathologic conditions, as has been

discovery of intercapillary glomerulosclerosis in the absence of glycosuria. The glucose tolerance test should be used to evaluate suspicious cases. This test becomes altered from normal to one approaching or resembling the diabetic as aging progresses. Goodof<sup>6</sup> found intercapillary glomerulosclerosis in 30% of non-diabetic patients over the age of 70 years, but stated that unfortunately the glucose tolerance test was not available for the material used in his study. In a similar number of non-diabetics between the ages of 5 and 25 years, evidence of intercapillary glomerulosclerosis could not be found.

Table 1 presents an analysis of the degree of involvement by a breakdown of the positive cases. The advanced lesion existed in 8% of the diabetics. Moderate involvement was present in 40%. Minimal changes accounted for

34%. Thus the advanced and moderate degree of involvement constituted 48% of the cases studied. This group of moderate or severe involvement is regarded as specific for diabetes. By including the group classified as minimal, the incidence of the lesion rises to 82% in our series, but concurrently the specificity falls as predicted by

tains a thin section of from 25 to 100 glomeruli. Therefore, failure to demonstrate the lesion after a study of a single section does not exclude the possibility of intercapillary glomerulosclerosis existing in the millions of unexamined glomeruli. It follows that examination of each glomerulus theoretically would provide the most accu-

TABLE 3. DEGREE OF INTERCAPILLARY GLOMERULOSCLEROSIS IN RELATION TO THE SEVERITY OF THE DIABETES.

| Degree of Diabetes | Degree of Sclerosis |          | Advanced | Total | %    |
|--------------------|---------------------|----------|----------|-------|------|
|                    | Minimal             | Moderate |          |       |      |
| Mild               | 8                   | 7        | 4        | 19    | 46.3 |
| Moderate           | 7                   | 9        | 0        | 16    | 39.0 |
| Severe             | 2                   | 4        | 0        | 6     | 14.7 |

Kimmelstiel and Porter<sup>9</sup>. The diffuse or minimal degree of involvement cannot be accurately distinguished from other glomerular changes, although we presume these changes are involved in the pathogenesis of the hyaline spherical lesions.

There are explanations for the divergence of reported incidence. It has been estimated that there are from 1 to 4 million glomeruli in each kidney. An average histologic preparation con-

rate appraisal of the incidence of intercapillary glomerulosclerosis.

Why certain diabetics have the renal lesion and others do not, has not been explained. Discovery of involvement of 48% hyaline lesions and 34% diffuse lesions in our diabetic series arouses conjecture. Intercapillary glomerulosclerosis possibly could be a constant accompaniment of diabetes mellitus. If we performed the ideal examination of all the glomeruli referred to above, the

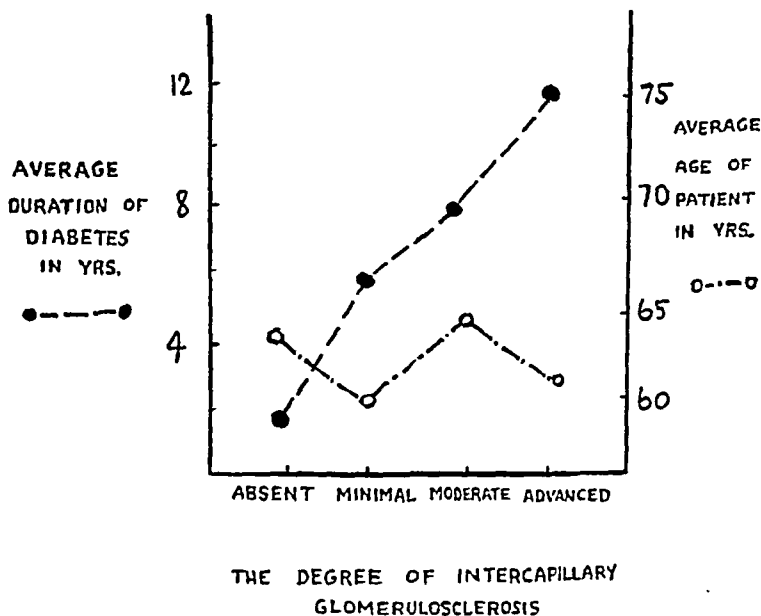


Chart 1. Relation to Duration of Diabetes and Age of Patient to Degree of Intercapillary Glomerulosclerosis.

lesion could conceivably be discovered in the remaining 18%. The pertinent problem of incidence has resolved itself to explanation of why the lesion is absent, rather than its presence.

There does not seem to be a marked predominance of the lesion in either sex. Females were 48% of all the diabetics examined while they comprised 54% of those presenting lesions of intercapillary glomerulosclerosis. Newburger and Peters<sup>13</sup> found 5 of 7 cases to be females. Herbut<sup>7</sup> reported 6 females and 3 males in his study of 9 cases. Goodof<sup>6</sup> believes the disease is more prevalent in women and states

more severe kidney complications than the person whose diabetes is controlled by diet alone? Is there a cause and effect relationship between the duration of diabetes and the advanced lesions, as there is in coronary sclerosis<sup>14</sup>? What role does insulin play in the pathogenesis of intercapillary glomerulosclerosis?

Table 3 demonstrates that almost half the kidneys with the hyaline lesion were from persons with mild diabetes. This group included the 4 kidneys with the advanced lesions. Severe diabetes, which was present in 24% of the entire group, accounted for

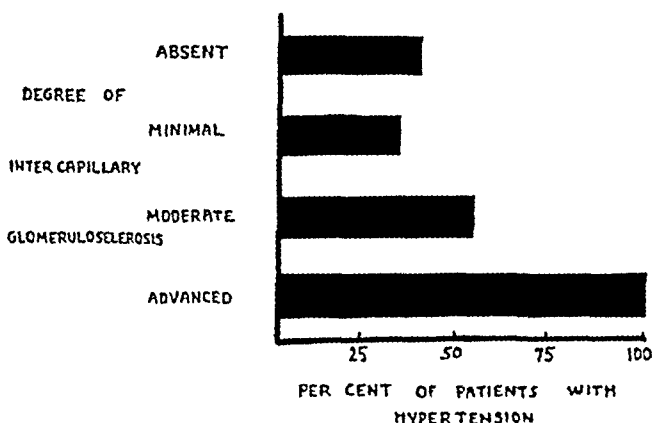


Chart 2. Incidence of Hypertension in the Different Degrees of Glomerulosclerosis.

a ratio of 7 out of 10. Other workers have reported a predominance in women over men varying from 30 to 60%. In our series 4 out of 5 diabetics were found to have the lesion. Thus the incidence of intercapillary glomerulosclerosis is closely related to the incidence of diabetes. The predominance of diabetes in the female can be expected to reflect in studies of sex incidence in intercapillary glomerulosclerosis. Given an equal number of male diabetics and female diabetics, we presume no predominance of the lesion will exist in either sex.

RELATION TO DIABETES MELLITUS. Does the severe diabetic suffer from

only 14.7% of the cases of intercapillary glomerulosclerosis. These facts suggest that severe diabetics do not develop the lesions more frequently nor do they tend to have the advanced type of intercapillary glomerulosclerosis.

Comparison of the incidence of intercapillary glomerulosclerosis with the known duration of diabetes mellitus reveals that in the group having diabetes over 15 years all had the renal complication. Similarly, Goodof<sup>6</sup> found a constant increase in the incidence of intercapillary glomerulosclerosis with increase in duration of diabetes above 6 years. However, Laipply, Eitzen and Dutra<sup>11</sup> did not find correlation

between either the presence or degree of involvement of the glomerular lesion with the known duration of diabetes mellitus.

In our series the average known duration of diabetes in the minimal lesion was 6 years (Chart 1), while those with advanced degree of involvement was 12 years. There is an ascending line when average duration of diabetes is plotted against degree of involvement, giving the impression that we are dealing with a steadily progressive disease. As demonstrated, the age factor is easily excluded from the pathogenesis. The chances for a person to develop kidney complications increase each year he lives with his diabetes, but is apparently unrelated to his age. The progression of the lesion is unrelenting and appears to be unaffected by therapy.

Insulin has been mentioned as a possible cause of the lesion<sup>17</sup>. The severe diabetic in our series was also the one who received the greatest amount of insulin. Since the factor of severity of diabetes does not affect progression of intercapillary glomerulosclerosis, insulin cannot be regarded as significant in the pathogenesis of the lesion.

**HYPERTENSION.** It has been estimated that 50% of all diabetics have hypertension<sup>18</sup>. In our study, 52% of the diabetics were hypertensive. The percentage was similar to this in those with no discernible intercapillary glomerulosclerosis, those with minimal and those with moderate involvement. In the group with advanced renal changes, however, all suffered from hypertension (Chart 2).

Goodof<sup>6</sup> discovered hypertension in 50% of 88 patients with intercapillary glomerulosclerosis. In most of the reports occurring in the literature shortly after the original publication, the presence of hypertension in the clinical syndrome was stressed. But

these reports usually concerned severe lesions corresponding to our group of advanced intercapillary glomerulosclerosis. Later workers included many cases on the basis of only moderate kidney changes.

Laipply and his associates<sup>11</sup> found no correlation between hypertension and the incidence or degree of involvement of intercapillary glomerulosclerosis. We agree with this conclusion on the basis of our findings in those kidneys minimally or moderately involved. Normal blood pressure is wholly consistent with the diagnosis of intercapillary glomerulosclerosis early in the course of involvement. However, the small group of diabetics who have advanced involvement are usually hypertensive.

To explain all hypertension in diabetes by the presence of the spherical hyalinized glomerular lesion would obviously be fallacious. Arteriolar sclerosis plays a significant part, as it does in non-diabetics, and presumably can adequately explain the hypertension in those cases which at necropsy show only minimal changes of intercapillary glomerulosclerosis.

**PROTEINURIA AND THE NEPHROTIC SYNDROME.** Correlation of proteinuria and edema with intercapillary glomerulosclerosis is difficult. Occasionally instances are found where there is generalized edema but less proteinuria than in cases with minimal swelling of the ankles<sup>7</sup>. Newburger and Peters<sup>13</sup> found that early in the course of the disease proteinuria was present in a varying degree but that terminally it was usually very profuse. Others have had similar experience. Mild lesions have often shown little or no proteinuria<sup>6</sup>, while series of patients with advanced lesions have been almost uniform in the excretion of large amounts of protein in the urine<sup>11</sup>.

Accurate statistical appraisal is difficult because there may be many com-



plicating factors obscuring true proteinuria on a basis of intercapillary glomerulosclerosis. Pre-renal causes for proteinuria in diabetes are common. Many in our group of cases were in congestive failure. Some had peripheral gangrene and a few were in coma due to ketosis. Arterial and arteriolar sclerosis may adequately explain a portion of the proteinuria found. Nevertheless, certain trends are apparent. In the groups of mild and moderate lesions many had no proteinuria while a few had severe proteinuria. There does not seem to be correlation

our cases with diabetic kidney damage. Examination of the type of renal lesion usually associated with the nephrotic syndrome revealed that in 3 patients the spherical hyaline changes were severe. In the other 2 the lesion was classified as moderate. The syndrome was not observed in the absence of intercapillary glomerulosclerosis. Since the syndrome was not present in conjunction with minimally involved kidneys, it is a sign of late intercapillary glomerulosclerosis. If the diagnosis of kidney change were made only when the classical picture of anasarca

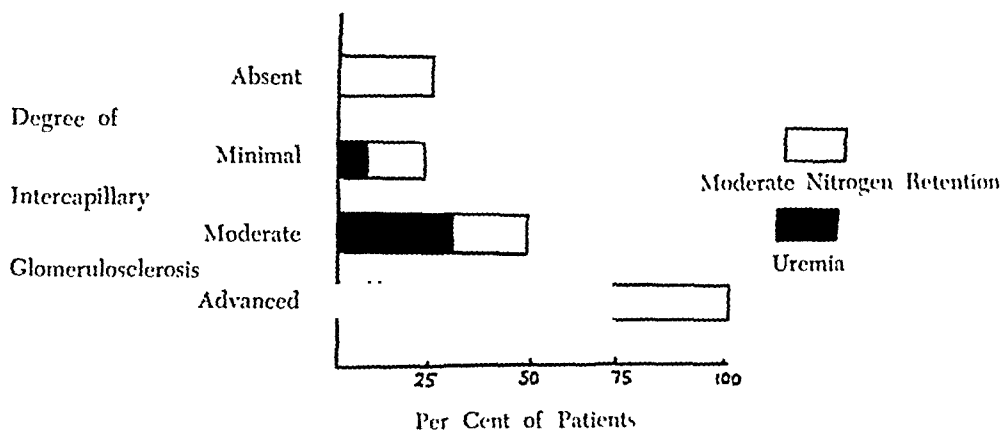


Chart 3. Incidence of Renal Failure in Relation to Degree of Intercapillary Glomerulosclerosis.

between the degree of the lesion and the amount of protein found in the urine, if the advanced lesions are deleted from consideration. The markedly advanced cases all had 3 to 4+ proteinuria. It seemed to be a fairly constant accompaniment of this type of lesion. While lack of proteinuria would be against the diagnosis of advanced intercapillary glomerulosclerosis its presence does not necessarily indicate severe involvement of the glomerulus.

The nephrotic syndrome, when it occurs, has characteristic features including proteinuria, low blood proteins, elevated blood cholesterol and universal edema. The nephrotic syndrome was present in 12.27 of

appeared, more than 4 out of 5 cases of the disease would be missed. The syndrome is of ominous prognostic significance. It indicates that the kidneys are hopelessly involved.

While morphologic study is not a complete method of estimating functional integrity of the kidney or any other organ, nevertheless certain conclusions seem justifiable. From the nature of the lesion it may be expected that the minimal stage presumably should not affect kidney function, while moderate glomerular involvement in the absence of other pathologic findings should leave the kidney with enough functional reserve to clear waste products efficiently. The advanced lesion, however, affecting

almost every glomerulus with marked hyalinization, sooner or later will lead to nitrogen retention. Severe uremia may possibly be precipitated with the addition of pre-renal factors such as cardiac failure or acidosis. Examination of Chart 3 confirms the ideas gained from the morphologic studies. As the lesion advanced in severity, the percentage of patients with moderate nitrogen retention and uremia showed progression until all the severe cases had either moderate kidney failure or uremia.

Proteinuria, edema resulting from hypoproteinemia and nitrogen retention are manifestations to be taken as evidence of advancing renal failure and not as significant signs of any particular disease of the kidneys.

**RELATIONSHIP TO THE ARTERIOSCLEROTIC PROCESS.** Arterial and arteriolar sclerosis is known to be related to diabetes mellitus. It has been demonstrated that progression of arteriosclerosis is accelerated by this disease. Coronary artery sclerosis is encountered more frequently in the diabetic than in the non-diabetic, and when coronary sclerosis is present it has a poor prognosis in the presence of diabetes<sup>18</sup>. Because of the possibility of renal vascular sclerosis being a causative factor, most papers on the subject have mentioned the high incidence of advanced cardiovascular sclerosis with intercapillary glomerulosclerosis. Newburger and Peters<sup>13</sup> believe the pathogenesis of intercapillary glomerulosclerosis is directly related to severe arterial and arteriolar degeneration. By contrast Siegal and Allen<sup>16</sup> excluded the possibility that the lesion is secondary to marked nephrosclerosis because of its presence in cases of diabetes without renal vascular complications. According to Herbut<sup>7</sup>, benign nephrosclerosis is an accompanying lesion in most cases, but he has seen examples especially in younger people where intercapillary

glomerulosclerosis is the only renal lesion. Since it is recognized that patients with mild diabetes do have accelerated vascular changes and that frequently the vascular changes are more pronounced in one area of the vascular tree than in another, Porter and Walker<sup>15</sup> suggested that capillary changes may represent another instance of predilected degenerative processes. Laipply, Eitzen and Dutra<sup>11</sup> recognized that those kidneys with the greatest degree of intercapillary glomerulosclerosis had the most pronounced vascular changes, but believed that the incidence would have to be expected, since intercapillary glomerulosclerosis is present in the same age group as persons with advanced sclerosis. They agree that it is contributory, but do not believe that it is the sole factor.

In our group of 50 non-diabetic kidneys, most of which were examples of nephrosclerosis, only 1 case with a spherical hyaline lesion was found. Causal relationship implicating vascular sclerosis is not suggested by this finding.

Arteriosclerosis obliterans was found in 50 of 100 diabetics selected at random by Pearl and Kandel<sup>14</sup>. This advanced arteriosclerotic degenerative process has been estimated to be 11 times as frequent in diabetics as in non-diabetics of comparable age groups<sup>5</sup>. Progression of arteriosclerosis obliterans ultimately results in gangrene. The high incidence of this complication in diabetics is well known. We compared far advanced peripheral arteriosclerosis, as roughly measured by the incidence of gangrene, with the degree of involvement of the kidney by intercapillary glomerulosclerosis. In the diabetic group which did not have any evidence of intercapillary glomerulosclerosis the incidence of gangrene was 22%. Of those with the diagnosis of intercapillary glomerulosclerosis, 24% had gangrene of an extremity, while of those having

the most advanced intercapillary glomerulosclerosis 25% had severe arteriosclerosis obliterans as measured by peripheral gangrene. These figures arouse speculation. Were vascular disease a prominent etiologic factor in intercapillary glomerulosclerosis, we would expect a higher incidence of gangrene in those with far advanced kidney disease. While correlation of pathologic processes by this method may be open to question, nevertheless the figures are of enough significance to be convincing. The basic importance of arterial and arteriolar sclerosis in causing intercapillary glomerulosclerosis seems most unlikely.

**Summary.** The literature reveals differences of opinions and theories concerning specific renal change in diabetes. The objective of this paper has been to reduce these opinions and theories to a concise presentation, and to correlate this with our own findings.

Recent reports have considered ever higher estimates of the incidence of intercapillary glomerulosclerosis in diabetics. The concept that intercapillary glomerulosclerosis is a frequent accompaniment of diabetes mellitus of

long standing is given support. In one decade this is a marked alteration in the knowledge of the pathology of the diabetic kidney.

Hypertension, proteinuria, the nephrotic syndrome and renal failure are shown to be unrelated to the involvement of the kidney, except in those few cases in which the lesion is far advanced. In the latter instance the components are usually found to make the clinical diagnosis of intercapillary glomerulosclerosis obvious. Before this stage is reached, we can only speculate on the amount of focal hyaline change that is taking place. It is reasonable to assume, however, that progression of the renal lesion will take place irrespective of therapy. With increase in the average length of life expectancy for well-controlled diabetics, we must be more aware of the pathogenesis and pathology of this complication of the metabolic disease.

Arteriosclerosis presumably is a separate problem in diabetes. While etiologic factors may be similar to those of intercapillary glomerulosclerosis, the pathogenesis of the two conditions at present does not appear to be closely related.

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# ALBUMINURIA IN SERVICE RECRUITS: A LABORATORY STUDY OF 193 CASES REFERRED FROM ROUTINE MEDICAL EXAMINATION

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THE occurrence of albuminuria in persons otherwise free from evidence of disease has presented a problem ever since its first discovery. Many observers have attempted to classify such cases and some of their publications, briefly reviewed here, show how diverse the significance of symptomless albuminuria may be. The present report summarises the results of our own observations, which have been made throughout a period of 7 years, 1942-48, and are derived from laboratory investigations of 193 young adults who, at their routine medical examination for recruitment into the Services, had all shown symptomless albuminuria. The subjects were referred to us for an independent opinion as to the probable significance of the albuminuria.

**HISTORICAL PERSPECTIVE.** In 1694 Dekkers discovered albumin in urine, making use of what is now the boiling test, but it was not until 1827 that Bright associated albuminuria with nephritis (see Dukes<sup>10</sup>). According to Young *et al.*<sup>32</sup> who have surveyed the literature, Becquerel<sup>5</sup> (1841) was the first to record albuminuria in a young adult, unaccompanied by evidence of renal disease; Vogel<sup>30</sup> (1864) noted a similar instance. "Remittent" albuminuria was first studied by Moxon<sup>21</sup> in 1878 and in the same year von Leube<sup>17</sup> published his finding that 4% of

apparently healthy soldiers had albumin in their urine. Pavy<sup>22</sup> described a so-called "cyclic" albuminuria, while Stirling<sup>27</sup> (1887) first proved the existence of a definite condition to which he accorded the term "postural albuminuria"; Teissier<sup>28</sup> (1899) called this same condition "albuminurie orthostatique". The benign nature of this type of proteinuria was doubted by Senator<sup>26</sup> (1904) who concluded that it indicated some degree of renal abnormality. In 1905 Dukes<sup>9</sup> recorded the presence of albumin in the urine of 16% of schoolboys and ascribed their proteinuria to instability of the cardiovascular system; when the subjects were later tested as adults they were all albumin-free. Jehle<sup>13</sup> concluded from a study of 300 children that their albuminuria was due to hyperemia of the kidney caused by lordosis of the lumbar spine. The production of albuminuria by severe physical effort was noted by Collier<sup>7</sup> when he tested the urine of each member of the Oxford boat crew in 1906, immediately after the race.

With regard to incidence, so far as young adults are concerned, McLeod and Ameuille<sup>20</sup>, in examining 2,000 soldiers, noted albuminuria in 2.9%, casts in the micro-deposit in 0.86% and red cells in 0.66%. MacLean<sup>19</sup> found albuminuria in 5.8% of 60,000 men, the incidence being the same in

a group of 10,000 before military training and in a group of 50,000 after training. The albuminuria was slight in 3%, considerable in 2.8%; while in only 1.1% was there an abnormal urinary micro-deposit. Theobald<sup>20</sup>, examining 5,000 Post-Office girls, noted albuminuria in 6.7%.

Lee<sup>16</sup>, Fox<sup>11</sup> and Bashford<sup>3</sup> have all concluded from long-term observations that adolescent albuminuria is a condition which does not develop into renal disease, and the benign nature of orthostatic albuminuria has been substantiated by the biochemical studies of Post and Thomas<sup>23</sup> and of Schultz and Swanson<sup>25</sup>. However, caution was expressed by Gulland<sup>12</sup> who believed that slight degrees of nephritis might often occur wherein renal efficiency tests alone failed to demonstrate defective kidneys. Moreover, Russell<sup>24</sup> pointed out that some instances of orthostatic albuminuria might represent a stage in resolving nephritis, especially of scarlatinal or diphtheritic origin, though Diehl and McKinlay<sup>5</sup> could find no statistical significance in the incidence of precursory diseases.

In 1941, Lyall<sup>18</sup> published results of his study of 110 men who showed albuminuria on more than one occasion when examined for recruitment to the Services. Other recent contributions include those by Young *et al.*<sup>12</sup> on orthostatic albuminuria; Ahronheim<sup>1</sup> and an annotation<sup>2</sup> on emotional albuminuria; and a leading article in the *Lancet*<sup>17</sup> on albuminuria in the young. Wolman<sup>21</sup> has also surveyed the whole problem and recorded valuable observations on 420 apparently healthy men (out of 22,000 entering the U. S. Maritime Service) who had proteinuria, mostly intermittent in type but persistent in 7 cases, significant of mild unsuspected nephritis in 5 cases and of urologic disease in 3 cases. Wolman also deduced that random urinalysis of single specimens will usually reveal

cases of nephritis though it will often fail to demonstrate cases of urologic or benign intermittent proteinuria. In studying such cases, the concentration of protein in random specimens of urine was not found to be diagnostically helpful. Our own observations were begun at the end of 1941 and continued to the end of 1948.

**Scheme of the Investigation.** The 193 subjects studied comprised 187 males and 6 females, all civilians, and referred from primary routine medical examination for recruitment into the Services. Their mean age was 19.7 years (standard deviation 4.8) and the range 14 to 43 years. Most of the subjects were age 17 to 24, though 14 had ages from 27 to 43 years and 2 cadets were aged 14. They had all shown albuminuria on 2 or more occasions at routine medical examination but none had clinical evidence of renal disease.

On arrival at the laboratory, each subject provided an initial (ambulant) urine, a first-hour specimen after sitting and a second-hour specimen after lying down. This procedure was found to be an adequate (but not rigorous) test for the existence of postural albuminuria. Although many of the patients brought with them a sample of urine passed on waking in the morning and these also were examined, especially for specific gravity and pigment concentration, no exclusive reliance was placed on the results, because there was no guarantee as to their origin or ownership. The initial (ambulant) urine was examined for the presence of red or white corpuscles or casts in the micro-deposit and all samples were tested for the presence of protein by the boiling test or with salicylsulphonic acid. Quantitative determinations of protein were carried out in selected cases. Blood urea concentration was determined by the method of King *et al.*<sup>14</sup> and urea clearance value by the procedure as described by Beaumont and Dadds<sup>4</sup>.

**Results.** The distribution of cases is shown in Table 1 where they are divided into 5 groups according to the type of albuminuria and the character of the micro-deposit. Of the total persons investigated, 53 showed no albuminuria when tested at the laboratory and their urine never contained red or white corpuscles or casts. It was noted that several individuals gave

a history of "colds" or sore throats at the time of their medical examination and altogether this group ("albuminuria-absent") is regarded as affording examples of transient, intermittent or emotional albuminuria, devoid of pathological significance, but forming a valuable (negative) control with which to compare the positive groups. These 4 groups correspond closely to Lyall's<sup>18</sup>, except that in our series all the nephritis cases are together, whereas Lyall divided his into subacute and chronic or subchronic.

noted in this group was 600 mg. per 100 cc.

The group where albuminuria is described as "due to nephritis" comprises 19 men. Of these, 8 had erythrocytes in the urinary deposit, 3 had granular or red cell casts, and 8 had both erythrocytes and casts. The albuminuria was constant in 9 cases, somewhat diminished by recumbency in 7 cases and completely abolished by recumbency in 3 cases. The highest urine protein concentration found was 400 mg. per 100 cc., a value notably

TABLE 1. DISTRIBUTION OF 193 CASES OF ALBUMINURIA IN 5 GROUPS

| Type of albuminuria | Present Series |     | Present Series |     | Lyall's Series |     |
|---------------------|----------------|-----|----------------|-----|----------------|-----|
|                     | No.            | %   | No.            | %   | No.            | %   |
| Postural            | 65             | 34  | 65             | 46  | 31             | 28  |
| Persistent          | 41             | 21  | 41             | 29  | 22             | 20  |
| Due to nephritis    | 19             | 10  | 19             | 14  | 45             | 41  |
| Due to infection    | 15             | 8   | 15             | 11  | 12             | 11  |
| Absent              | 53             | 27  |                |     |                |     |
| TOTAL               | 193            | 100 | 140            | 100 | 110            | 100 |

TABLE 2. SUMMARY OF BIOCHEMICAL FINDINGS IN 5 GROUPS OF 193 CASES OF ALBUMINURIA.

| Type of Albuminuria | No. of Cases | Blood Urea<br>mg. per 100 cc. |      | Abnormal<br>Blood Urea<br>Values                    | Urea Clearance<br>% of normal |      | Abnormal<br>Urea Clearance<br>Values |
|---------------------|--------------|-------------------------------|------|---|-------------------------------|------|--------------------------------------|
|                     |              | Mean                          | S.D. |   | Mean                          | S.D. |                                      |
| Absent              | 53           | 28                            | 6    | 44 <sup>1</sup>                                     | 114                           | 34   |                                      |
| Postural            | 65           | 28                            | 7    | 44 <sup>2</sup>                                     | 123                           | 37   | 35 <sup>2</sup>                      |
| Persistent          | 41           | 28                            | 6    |   | 114                           | 24   |                                      |
| Due to nephritis    | 19           | 35                            | 9    | 60 <sup>3</sup> , 43 <sup>4</sup> , 46 <sup>5</sup> | 95                            | 45   | 29 <sup>3</sup> , 39 <sup>4</sup>    |
| Due to infection    | 15           | 31                            | 8    | 47 <sup>6</sup> , 42 <sup>7</sup>                   | 99                            | 41   | 31 <sup>6</sup>                      |

In the group "postural albuminuria", the characteristic features were an insignificant micro-deposit and an initial albuminuria which became completely abolished by recumbent posture. The highest urine protein concentration recorded was 1,100 mg. per 100 cc.

In the group "persistent albuminuria" there was likewise an insignificant micro-deposit throughout. Excretion of protein was continuous, though it was often lessened by inactivity and further diminished by recumbent posture. The highest urine protein concentration

less than that found within the groups where albuminuria was considered to be devoid of pathological significance. All the cases in the nephritis group are thus seen to have been characterised by the nature of the micro-deposit, while in most of them there was also a persistent albuminuria as well. In 3 instances within this group, confirmatory evidence of renal functional impairment was also obtained by biochemical tests.

In the last group, "albuminuria due to infection", 12 subjects out of 15

showed a persisting albuminuria while 3 had protein-free urine after recumbency. The highest protein concentration noted was 80 mg. per 100 cc. urine. In the micro-deposit, 9 had red corpuscles, none had casts, but all showed a significant number of pus cells. Cultures yielded *B. coli* from 4. *Proteus vulgaris* from 1, while microscopic search revealed *M. tuberculosis* from 1 and *N. gonorrhoeae* from 1. The remaining 8 urines yielded inconclusive results from bacteriological studies but were regarded as containing indirect evidence of infection.

Table 2 summarizes the biochemical data; blood urea and urea clearance figures are recorded as mean values with standard deviations for each group. Using the critical levels defined by Mean  $\pm$  2.S.D., afforded by the control group "albuminuria absent", a number of abnormally high blood urea values (over 40 mg. per 100 cc.) and low urea clearance values (under 46%) are noted for special consideration. These abnormal values characterized 7 subjects with high blood urea concentrations; of these, 4 had also abnormally low urea clearance values. More complete details of these 7 cases are recorded in Table 3.

**Discussion.** In Table 1 the numerical distribution of cases in Lyall's<sup>14</sup> series is noted alongside ours for comparison. The greatest differences are seen in the group "postural albuminuria" where our proportion is higher and in "albuminuria due to nephritis" where our proportion is lower. Since Lyall's tests for postural albuminuria were more rigorous than ours, in that his tests for absence of protein were done on overnight samples whereas ours were made with only 1 hour recumbent specimens, it would seem that the different proportions of "postural albuminurias" arise merely from chance in the samples of population studied. Any difference arising from

TABLE 3. DETAILS OF 7 CASES CHARACTERIZED BY ABNORMAL BIOCHEMICAL FINDINGS

| Case No. | Age | Sex | All albuminuria | S | L | RBC | Micro-Deposit WBC | Casts | Blood Urea mg. per 100 cc | Urea $\dagger$ Clearance % of normal | Type of Case                |
|----------|-----|-----|-----------------|---|---|-----|-------------------|-------|---------------------------|--------------------------------------|-----------------------------|
| 1.       | 18  | M   | +               | + | + | +   | —                 | —     | 44                        | (76)                                 | Blood urea not significant. |
| 2.       | 17  | F   | +               | + | + | +   | —                 | —     | 44                        | 35                                   | 6/12 post-nephrectomy.      |
| 3.       | 21  | M   | +               | + | + | +   | —                 | +     | 60                        | 29                                   | Nephritis.                  |
| 4.       | 17  | F   | +               | + | + | +   | —                 | —     | 43                        | 39                                   | Nephritis.                  |
| 5.       | 15  | M   | +               | + | + | +   | —                 | +     | 46                        | (71)                                 | Nephritis.                  |
| 6.       | 15  | M   | +               | + | + | +   | +                 | —     | 47                        | 31                                   | Pyuria.                     |
| 7.       | 15  | M   | +               | + | + | +   | +                 | —     | 42                        | (32)                                 | Pyelonephritis.             |

A = Ambulant, S = Sitting, L = Lying down.  
 $\dagger$  Urea clearance values in brackets are not significantly diminished.

the procedure adopted would have tended towards the finding of a smaller proportion of postural type in our series instead of the larger proportion which was, in fact, found.

It is noteworthy that our group of nephritis cases did not include any individuals with clinical evidence of nephritis, whereas that of Lyall did. If those with "clinical" nephritis are segregated, a remaining 21% of Lyall's patients appear as having asymptomatic albuminuria due to nephritis. This percentage is now comparable with our figure of 14%.

Finally from Table 1 it is seen that the proportion of individuals whose albuminuria was attributed to infection was the same in Lyall's series and in our own.

The results of the biochemical investigations, as summarized in Tables 2 and 3, show abnormally high blood urea concentrations in 7 cases, accompanied in 4 instances by abnormally low urea clearance values. Regarding Table 3, it may be noted that Case 1 showed a slightly raised blood urea which was ultimately discarded as clinically insignificant, while Case 2, a postural albuminuria, had abnormal values ascribed to previous nephrectomy. Of 3 cases of nephritis with raised blood urea, 2 showed also a diminished urea clearance; while of the 2 cases of infection with raised blood urea, 1 showed a diminished urea clearance.

The urea clearance test is generally regarded as more sensitive than any other for assessment of renal efficiency. It is simple to perform yet superior to a blood urea estimation alone. Moreover, in some cases of nephritis, diminished urea clearance values may be found, when the blood urea concentration is within normal limits, though results of this type did not happen to occur within our series. Whenever renal insufficiency was detected by bio-

chemical examinations there was also substantiating evidence from a study of the albuminuria itself or of the urinary micro-deposit. However, it is evident from Table 3 that Case 4 might easily have been passed as a persistent albuminuria (without nephritis) if the biochemical tests had been omitted, and the few red corpuscles in the micro-deposit not accorded any significance. Similarly, Case 5 might have appeared to be a postural albuminuria had the biochemical tests been omitted and the micro-deposit overlooked.

Although in our series of patients with simple persistent albuminuria no instances of renal functional impairment were discovered by biochemical examinations, persistent albuminuria was invariably regarded with suspicion and the possibility of renal disease carefully considered. An illustration of the correctness of this view is a case described by Brown and Ginsberg<sup>6</sup> of a woman who had perennial albuminuria for 46 years after scarlet fever at the age of 9. She died at age 55 of left ventricular failure and chronic glomerulonephritis was demonstrated at autopsy.

**Conclusions.** It is thus concluded that while a persistent albuminuria together with an abnormal urinary deposit provides immediate evidence of renal disease, an albuminuria significant of organic disease may show considerable variation with changes in posture. Determinations of the protein content of the urine are valuable in studying these changes but the protein concentrations themselves possess no diagnostic significance.

When a patient shows any degree of albuminuria in the recumbent position or shows a micro-deposit which is at all suspicious, a urea clearance test may provide further evidence of disease and its performance is therefore advisable. The result of such



a test, in conjunction with the albuminuria and microscopic evidence, will reveal the occasional case of renal disease which may otherwise go undiscovered. On the other hand, when a proteinuria of postural type is definitely demonstrated and the urinary deposit is above suspicion, renal function tests are not necessary for they will not contribute any indication of kidney disease.

**Summary.** Previous studies of albuminuria, its types, origin and significance are briefly reviewed in historical perspective.

A laboratory investigation of 193

cases of symptomless albuminuria is recorded, the subjects being referred from primary routine medical examination for recruitment into the Services.

A determination of the type of albuminuria and the nature of the micro-deposit is shown to afford a means of selecting those cases in which the urea clearance test is also likely to be of value.

It is concluded that this scheme of investigation provides the evidence necessary for the medical grading of individuals who have albuminuria but otherwise appear clinically to be healthy.

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# ACRONECROSIS DUE TO FIBRIN THROMBI AND ENDOTHELIAL CELL THROMBI

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CYANOSIS followed by necrosis of the extreme parts of the periphery ("Acra") such as the tip of the nose, the lobe of the ear or the tip of a finger, is an event well known to occur in subacute bacterial endocarditis. It is suggested that the term "Acronecrosis" be adopted to describe this phenomenon. Its usual explanation by embolism from distant sites appears to be unsatisfactory in many cases in the light of the findings recorded in this paper. These findings concern locally arising fibrin *thrombi* in post-capillary vessels as observed in 2 such cases. A comparison will be made with the vascular changes in 3 other cases: 1 of subacute bacterial endocarditis without acronecrosis, 1 of unexplained purpura and 1 of fulminant tuberculous septicemia. Finally, the relationship will be discussed with a variety of mural changes in smaller vessels as seen in generalized diseases such as Dermatomyositis, Lupus erythematosus disseminatus and Polyarteriitis nodosa.

**Case Abstracts.** CASE 1. A man aged 39, 5 years ago, had subacute rheumatic fever. It involved most joints and followed on tonsillitis. One year ago, he had sudden severe pain in left knee; 3 months ago shingles in right leg and pain, while rash was present. Since then, general weakness and development of clinically typical subacute bacterial endocarditis, the most striking feature of which was the symmetrical spread of small hemorrhages with necrotic centers in both ears, right arm, shoulders and big right toe; that is, the picture of "Acronecrosis".

**Biopsy No. S.D. 1988** Skin (from necrotic area) of 1 finger of the right hand: In the cutis many dilated capillaries and venules are filled with thrombotic material (Fig. 1).

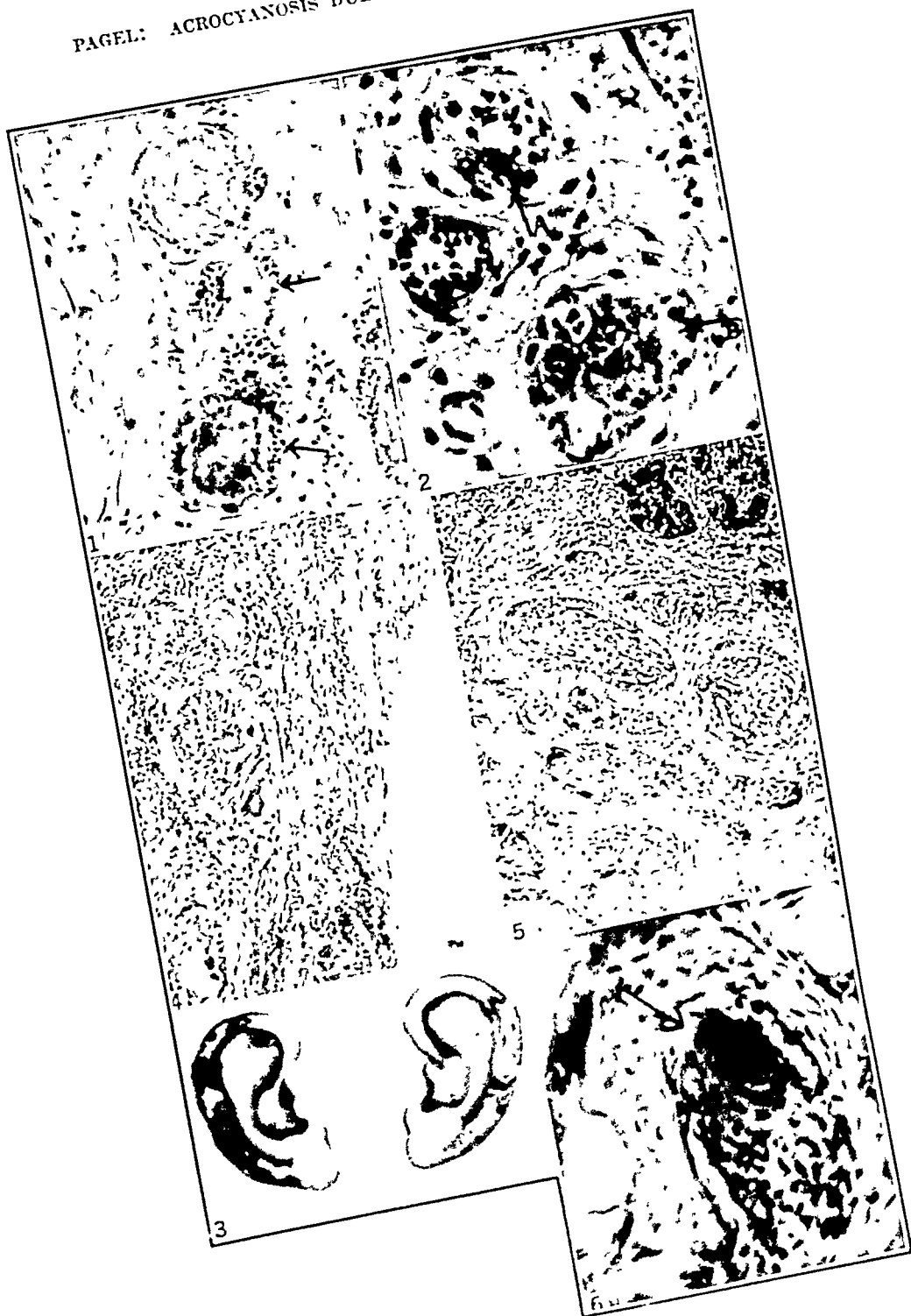
the latter usually forming projections of fibrinoid material into the lumen rather than occluding plugs. Sometimes the clot, whether or not endothelialized, bridges the whole lumen effecting partition, or adheres to a thickened intima in which endothelial elements appear to be swollen and proliferating (Figs. 1 and 2). Some of the fibrin-thrombi show an admixture of what appears to be proliferating and desquamated endothelial elements and mononuclear cells.

In one vessel, which is horseshoe shaped in cross section, fibrinoid material lines the entire convex surface.

**NECROPSY No. 43-221.** Irregularly distributed petechiae, notably in the skin of the right hand (including fingers), at the right fore-arm, right toe and in both ear lobes. **Larynx:** Edema and petechiae in the region of left part of the ventricular and vocal cord. **Heart:** Small area of granular vegetations on lateral cusp of tricuspid valve. **Mitral valve:** Two areas, each 2 x 1 cm., of grape-like vegetations. Parietal endocarditis on posterior wall of left ventricle. **Spleen:** Enlarged (14 x 8 x 5 cm.). Almost fluid, dark red on cut section and adherent to adjoining organs. **Kidneys:** 14 x 8 x 44 cm. Capsule strips easily. Surface variegated, with petechiae—the picture of "focal embolic nephritis".

**BACTERIOLOGY:** Spleen grew *H. influenzae* pure culture.

**HISTOLOGY:** **Myocardium:** 1, large fibrotic scars; 2, extensive parietal thrombosis; 3, formations of granulomata in the parietal endocardium beneath the thrombus, with large mononuclear elements, not unlike those seen in Aschoff nodules; 4, almost all the arterioles contain thrombotic material. While in the majority of vessels this material completely plugs the lumen or lies free in its centre, in a few arterioles the clot is eccentrically placed, occupying less than two-thirds of the lumen and fused with the vessel wall. Sometimes there is endothelial cover, but no ingrowth of endothelial cells to suggest that organization has led to the parietal adhesion. **Peripheral Muscle:** Areas of vacuolar degeneration of muscular substance with prolifera-



tion of muscular repair cells forming granulomata. *Kidney*: Fibrinoid conglutination of segments of glomerular tufts and also of afferent arterioles, as seen in "embolic focal nephritis". Some interstitial hemorrhages. *Spleen*: Small area of hemorrhagic necrosis. necrosis.

**Comment on Case 1.** With regard to the skin changes, the following features are noteworthy: 1, Symmetrical distribution in both ear lobes and shoulder regions; 2, The predilection of lesions for "Acra"; that is, areas in the extreme periphery where circulatory stagnation is most likely to obtain. On clinical grounds alone, therefore, the usual explanation of the small hemorrhages and areas of necrosis in subacute bacterial endocarditis (that is, by embolism), appears unsatisfactory. The fresh granular appearance of the fibrinoid material unaccompanied by organization and yet firmly fused with the vessel wall suggests strongly that this has been a local thrombosis.

**CASE 2.** Male, aged 30, had rheumatic fever at 6 years with signs of rheumatic carditis until 12.

Latterly developed subacute bacterial endocarditis with slowly progressing hemorrhagic necrosis, affecting the outer fringe of the helix of the ears (Acronecrosis) (Fig. 3). The full details of this case are reported elsewhere (Dr. K. P. Ball).

**BIOPSY FROM THE LEFT EAR.** (March 27th, 1947; two and a half months before death): The ulcerated area shows fibrinoid necrosis of the upper layer with a fairly sharp lower margin but very little cellular infiltration along the junction line. Deeper, in the surviving tissue, there are nodular perivascular aggregations of lymphocytes. In the living zone, there are many greatly dilated

capillaries, some of which contain small projections of endothelial-covered fibrinoid material (Fig. 4), and in a few vessels the lumen is completely filled by the mass.

**NECROPSY No. 47-205.** Tall thin man with slight clubbing of the fingers. No petechiae. There is ulceration of the helix of both ears with some adjacent cyanosis. *Brain*: There is a recent hemorrhagic softening, 1 cm. in diameter, in the right parietal cortex involving the white matter only. There is also a fluid filled space 2 cm. in diameter in the right occipital region. *Heart*: Enlarged, 460 gm. Aortic conus 8 cm. wide. Left ventricle: length from apex to aortic conus 10.5 cm. Left ventricular wall, width 1.3 cm. In the apex and part of the septum there is old and fresh infarction with aneurysmal dilatation. The aortic valve is bicuspid and shows cauliflower vegetations on both cusps, each about 0.5 cm. long. These are hard but easily crumbled. The anterior descending branch of the left coronary artery shows a zone of fibrous narrowing with occlusion about 3 cm. from its origin, but distally the lumen is patent. On the posterior cut surface of the ventricular wall there is myocardial fibrosis.

**HISTOLOGICAL EXAMINATION.** *Myocardium*: Some old fibrotic scars and one small area of recent perivascular infiltration with chronic inflammatory cells. *Helix of left ear*: The picture is now quite different from that seen a few weeks before in that the larger (probably arterial) vessels show changes of fibrotic obliteration and recanalization (Fig. 5). The only fibrinoid material seen occurs as small patches enclosed in the fibro-vascular tissue. *Kidney*: Chronic "focal embolic nephritis" with patchy fibrosis of glomeruli.

**Comment on Case 2.** As in the previous case, the bilateral nature of Acronecrosis and its gradual development argue against an embolic mechanism. Likewise, the histological picture in the biopsy of sessile and polypoid

FIG. 1. CASE 1. Capillaries of the skin of finger containing fibrinthrombi, some producing partition of vascular lumen. x 250. In this and subsequent figures, magnifications have been slightly reduced for purposes of reproduction.

FIG. 2. CASE 1. Skin. A., a small fibrin thrombus endothelialized and becoming incorporated into the intima simulating fibrinoid infiltration of the latter. B., fibrin thrombus partly endothelialized causing multipartition of vascular lumen. x 375.

FIG. 3. CASE 2. Acronecrosis of Helix on both sides.

FIG. 4. CASE 2. Biopsy from Helix. Ulcerated area with many venules containing fibrin thrombi being endothelialized. x 100.

FIG. 5. CASE 2. Helix. Material removed at autopsy, 10 weeks after biopsy. Picture of organised and recanalised clots. x 90.

FIG. 6. CASE 3. Capillary with fibrinoid infiltration of intima. x 375.

projections situated in the venous sinuses points to local formation.

If only material from necropsy had been available, the appearances there of organization and recanalization might well have supported the interpretation of the whole process being the result of previous embolism.

**CASE 3.** A female factory worker, aged 23, had given up work for 2 years because of ill health. One year before admission she was found to have a presystolic murmur and a radiograph suggestive of mitral stenosis.

During the last 3 months, pain in left foot and dyspnea. Obese, cyanosed, young woman, mentally slow. *Fundi:* marked sclerosis of arteries with innumerable petechiae along vessels and papilledema. In right fundus large white-yellow, ? degenerative areas. Gross defects in peripheral areas of fields of vision, complete color blindness. ? Subacute nephritis. Died of heart failure.

**NECROPSY 44-103.** A very obese, cyanotic and edematous young woman. No changes in brain and pituitary. Tongue smooth. Complete, probably embolic, obstruction of main branch of right pulmonary artery. *Heart* (1000 gm.): Gross dilatation of right side and

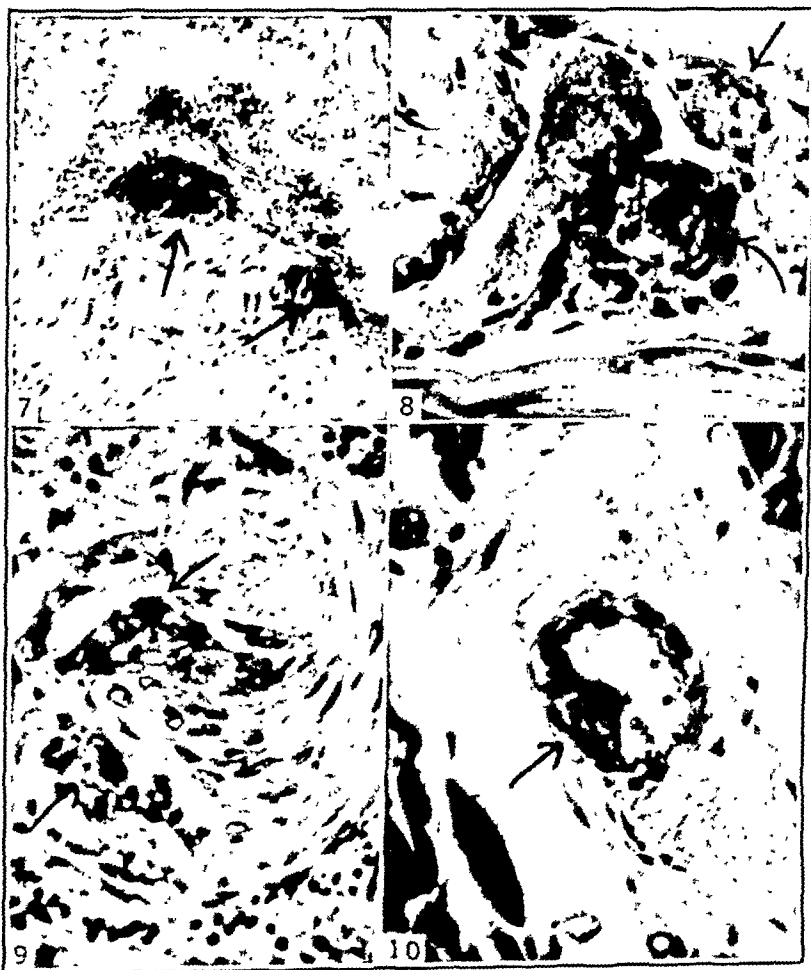


FIG. 7. CASE 3. Lung. 2 small fibrin-thrombi, 1 nearly organized by endothelial syncytia.  $\times 110$

FIG. 8. CASE 3. Heart muscle. Endothelialized fibrin-thrombi with endothelial proliferation  $\times 600$ .

FIG. 9. CASE 3. Lung. Bipartite arterial branch with fresh fibrin-thrombi and endothelial cell proliferation  $\times 620$ .

FIG. 10. CASE 3. Myocardium. Fibrinoid infiltration of intima  $\times 700$ .

auricular appendage filled with thrombotic material. Tricuspid free of vegetation. Posterior cusp of mitral valve covered with easily removable red-currant sized vegetations. Valve itself not thickened or shrunken. Myocardium on cut surface without changes. Aortic valves and aorta free. Right femoral vein thrombosed in its whole length. Passive venous congestion of liver and spleen. From the latter *Streptococcus viridans* (scanty growth) recovered. *Kidneys*: variegated; picture of a diffuse subacute nephritis.

**HISTOLOGICAL EXAMINATION.** *Right auricle*: Some large scars with marked edema. Some medium sized arteries obliterated by recanalized plugs with fibrinoid centres. Myocardium of the left ventricle: Precapillary arterioles blocked by typical emboli, others by old recanalized plugs, some of which still exhibited fibrinoid patches in the centres. A number of arterioles, however, showed different changes, namely, fibrinoid swelling of the intima at one side or corner of the circumprotruded into the lumen—not unlike a polypus pushing the endothelial lining forward. In some arterioles, the whole lumen was filled by a hyaline patch with only a few persisting narrow capillary slits.

In these changes 2 processes seem to be involved: 1, Formation of a plug of fibrinoid material which, by organization, becomes part of the vascular wall and subsequently covered by endothelium. 2, Fibrinoid swelling of the vascular wall itself (Figs. 6 and 7). Both these processes were also conspicuous in the tongue, where the frequency of occurrence is second only to the myocardium. Here a stretch of the same vessel may reveal fibrinoid swelling of its wall on one side and a polypoid thrombus narrowing down the lumen on the other. In other small arteries alongside the polypoid mass there is desquamation and proliferation of the endothelium and edematous swelling of the intima (Fig. 8). In the neighborhood of the more superficial vessels of the tongue, the subepithelial collagenous layers show changes which may well be a consequence of the vascular changes. The fibers are separated by edema or show swelling with loss of the usual staining reactions—orange with Mallory or Van Gieson; nonetheless, the argentaffin fibrils are apparently intact. In addition to these focal areas of upset of collagen in relation to affected vessels, there are throughout the body, strikingly so in the diaphragm, larger ill-defined zones of damage to collagen.

Gross changes were also observed in the finer branches of the *Pulmonary Artery*. These were: 1, Old changes showing the peculiar

partitioning of the lumen as seen in late rheumatic arteritis (Von Glahn and Pappenheimer<sup>1</sup>, 1926); in this 2 or more, and up to 7, lumina are formed by intimal septa from the subendothelial layers while the internal elastic membrane remains apparently unaltered (Fig. 9). In addition, there are frank organized clots projecting like polypi in the larger arterial branches. 2, Fresh changes, namely circumscribed fibrinoid swelling of the intima associated with proliferation of peculiar large cells, probably endothelial (Fig. 9). Such swellings and proliferation of cells are particularly evident where the fresh lesion occurred on top of the old changes inside the partitioned lumen of the artery.

In the kidneys some glomeruli exhibited crescents typical of subacute glomerulonephritis, others the "wire loop" pattern as described in Lupus Erythematosus (Klemperer *et al.*<sup>5</sup>, 1941).

**Comment on Case 3.** The various histological changes observed in this case can be traced back to; *a*, lesions of the intima, namely, a plaque-like fibrinoid swelling in the wall which usually occurs on only one side of the vessel. This intimal lesion is most severe in the arterioles of the myocardium, tongue and lungs; *b*, small projecting cushions or polyps of the intima, usually with a core of fibrinoid material and an associated desquamation or proliferation of the endothelium.

**CASE 4.** Woman aged 74 years. Weakness for a month; for 3 or 4 days purple spots on arms and legs. Admitted comatose. Obese jaundiced woman with stertorous breathing. Blood platelets, 60,000; Hemoglobin, 50%; red blood cells 3,060,000 per c. mm.; white blood cells, 14,500 per c. mm. Diagnosis: Thrombocytopenic purpura.

**NECROPSY 44-125.** Stout old woman with generalized purpuric eruption. Small hemorrhage, 2 x 1 cm., in left cerebellar cortex. Confluent bronchopneumonia in right lower and middle lobe. Flabby myocardium, no valvular changes. Atrophic gastric mucosa. Small rusty colored liver. Large soft spleen, pattern invisible on cut surface. Femur marrow soft, hyperplastic, raspberry colored. *Kidneys*: no appreciable naked eye changes.

**HISTOLOGICAL EXAMINATION.** *Heart*: In addition to old triangular scars, extensive changes are found in the small arteries and arterioles. These show hyaline thickening of

the intima, as a rule on one side of the circumference only. There were hardly any additional perivascular changes.

The other organ in which similar vascular changes are most prominent is the *suprarenal*, including the surrounding fat tissue. Not only fresh hyaline infiltration of the intima (chiefly on one side of the vascular circumference), but also fibrous intimal cushions are present, obviously the end result of intimal granulomata, and finally arteries with a double lumen not unlike those found in the lungs of Case 3. The *spleen* and *kidneys* both show hyaline deposits in the intima of the arterioles and there is some hyaline thickening of glomerular capillaries with occasional crescents.

Hemorrhages in the *skin* and *brain* were extensive, but no vascular changes comparable to those described above were discovered. The active femur marrow contained a considerable number of apparently normal megakaryocytes.

**Comment on Case 4.** This is a case of purpura associated with widespread arteriolar disease without obvious cause. The picture differed from that of the preceding cases in the absence both of fibrinoid infiltration and of valvular vegetations as a possible source of emboli.

**CASE 5.** Male, aged 51. An instance of fulminant tuberculous septicemia reported in detail elsewhere (Blair and Pagel<sup>1</sup>, 1917). This case is mentioned because the arterial capillaries of the myocardium show fibrinoid infiltration involving the intima on one side of the vascular circumference (Fig. 10). These changes are identical with those observed in Case 4 and some of those in Case 3.

The localization of the arteriolar changes in the myocardium in the absence of clinical hypertension or any vascular changes in kidney, spleen or pancreas seem to indicate similarity with the previous cases.

**Discussion.** The vascular changes in these cases are of 2 types: 1, Small fibrinocellular thrombi found in venules of the skin and occasionally in arterioles, notably of the lung. In the skin, the thrombi had caused multiplication of some of the venules. It is reasonable to assume that a similar process can take place in small arteries of the lung

with the final result of a picture not unlike the "specific lesions of peripheral blood vessels in rheumatism" described by von Glahn and Pappenheimer<sup>1</sup> (1926). 2, A hyaline-fibrinoid infiltration in the intima of arterioles.

Type 1 is suggested as the explanation accounting for at least some of the cases of "acrocyanosis" and "acrocrosis" in subacute bacterial endocarditis. This type corresponds exactly with the lesions described by Oppenheim<sup>9</sup> (1921) and Ceelen<sup>2</sup> (1926) in typhoid fever, by Siegmund<sup>11,12</sup> (1923, 1925) in a variety of spontaneous (notably streptococcal) and experimental infections, and by Pagel<sup>10</sup> (1926) in tuberculosis of the experimental animal. Their experimental reproduction by repeated intravenous administration of microorganisms (staphylococci, *B. coli*, typhoid or tubercle bacilli) which are, however, not demonstrable in the vascular lesion, suggests that they are connected with a bactericidal and cleansing action situated in the endothelium. Later, the small thrombi are organized, forming intimal granulomata and finally scars. In typhoid fever and tuberculosis it is possible to find a range of vascular lesions, focal necrosis, fibrinoid and monocytic thrombi, intimal granulomata and scars. In subacute bacterial endocarditis the association of fibrinoid thrombi with numerous large mononuclear cells in the capillaries of the extreme periphery such as the ear and fingers is very obvious. This abundance of mononuclear cells may be interpreted as a sequel to the generalized endothelial cell proliferation and the fibrinoid nodules in the peripheral capillaries may also be secondary to endothelial proliferation. It may be mentioned, however, that fibrinoid nodules without associated endothelial proliferation have been produced in the endocardium by the injection of *B. coli* in vaccinated rabbits (Masugi and Isibasi<sup>7</sup>, 1936).

Both the experimental and human

evidence suggest that we are dealing with an immunological phenomenon associated with local fixation and digestion of organisms by endothelial and blood elements. It is suggested that first endothelial cells are destroyed and their debris, together with deposits of fibrinoid material or fibrin, form a small mass adherent to the wall; this is soon endothelialized and organized, to give the intimal granuloma. Where the mass is very small and not projecting it may well give the impression of a fibrinoid thickening of the intima. We thus have a picture not unlike that observed in polyarteritis nodosa, subacute bacterial endocarditis (*e.g.*, Masugi and Isibasi<sup>8</sup>, 1937, Fig. 9), disseminated lupus erythematosus (Klemperer *et al.*, 1941), dermatomyositis (Pagel, Woolf and Asher<sup>10a</sup>), and the response to intradermal injection of heat-killed streptococci in rheumatic fever patients (Humphrey and Pagel<sup>4a</sup>). The incorporation of these small fibrinoid masses into the wall is well seen in Cases 1 and 3, and it is only with care that they can be distinguished from the fibrinoid infiltration of the intima seen in Cases 4 and 5. It is, however, not suggested that fibrinoid infiltration of the intima is normally the product of the organization of fibrin thrombi. It is often an independent change and

also believed to be of immunological origin (Masugi and Isibasi<sup>8</sup>, 1937).

Finally, the location of the fibrin thrombi in extreme parts of the periphery ("Acra"), as seen in Cases 1 and 2 may be explained by a predisposition of these parts to thrombosis, as seen for example, in frostbite, in which hyaline and agglutinated thrombosis is the essential change (Lange, Weiner and Boyd<sup>6</sup>, 1946; Friedman and Kritzer<sup>3</sup>, 1947).

**Summary and Conclusions.** 1, In two cases of subacute bacterial endocarditis small fibrin thrombi and endothelial cell thrombi in the venous sinuses of the skin are described as the cause of Acronecrosis.

2, Similar fibrin thrombi and endothelial cell thrombi were observed in the smaller branches of the pulmonary artery in a third case of subacute bacterial endocarditis.

3, Organization of fibrin thrombi and endothelial cell thrombi can lead to fibrinoid and hyaline thickening of parts of the vascular wall or to multi-partition of a vessel owing to organization of multiple such thrombi.

4, Necropsy and experimental evidence suggest that the vascular changes described are due to a hyperergic response to antigenic stimuli.

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# THE ADMINISTRATION OF HISTAMINE DURING PREGNANCY: APPARENT LACK OF A CLINICAL OXYTOMIC EFFECT WITH SMALL DOSES

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IN the course of a prolonged program of clinical investigation and treatment of the so-called vascular diseases, allergic diseases and certain atypical pain patterns not amenable to more usual forms of treatment, we have had occasion to administer or to prescribe the administration of histamine in relatively small doses by the intravenous or subcutaneous route to 15 pregnant women. The question of the wisdom and the safety of using this drug in pregnancy has arisen. It has been pointed out that not only was histamine first derived from ergot but, in the past, it has actually been used as a uterine stimulant. In addition, the recent obstetric<sup>9</sup>, physiologic<sup>26,32</sup>, pharmacologic<sup>7,31</sup> and endocrinologic<sup>20</sup> literature continues to discuss the oxytomic effect of histamine in women and in female animals. As recently as 1946, editorial comment in the "Obstetrical and Gynecological Survey" was a reminder that histamine "exerts a powerful stimulating effect directly on the myometrium." Indeed, an impressive array of experimental literature may be found to document this opinion. In view, therefore, of the theoretical and apparent hazards of histamine therapy during gestation, and because of the absence of any undesirable sequelae of such treatment in our series of cases, we wish to record our observations. In addition, we wish

briefly to review some of the significant contributions of earlier workers relating to the oxytomic effect of histamine and to the general concept of histamine metabolism in pregnancy. Such data, to our knowledge, have not been gathered together in any recent review. This material will serve as a convenient prologue to our clinical notations.

**Review of the Literature.** Hofbauer<sup>12</sup> in 1926 studied the effects of acute histamine poisoning in pregnant guinea pigs. He observed a number of phenomena that were similarly noted in premature separation of the normally implanted placenta. Uterine spasm was one of the most consistently observable responses.

Bourne and Burn<sup>4</sup>, in 1927, by utilizing intra-uterine bags with manometer attachments in parturient women, demonstrated that histamine injected subcutaneously in a dose of 2.0 mg. (reckoned in terms of histamine base present) produced powerful but short-lived uterine contractions. With doses of less than 1.0 mg., no certain change in the intensity of the uterine movements was seen but an increase in the frequency of the contractions for a period of 30 minutes was encountered. It seemed as though the dose of 2.0 mg. exhausted the uterine musculature, because a period of quiescence followed the heightened

activity, and the effect, powerful as it was, did not shorten the course of labor. The dilatation of the cervical os was not greater at the end of the effect than at the beginning. The effect of the injection of a dose of 2.0 mg. appeared within 1 minute and the intra uterine pressure rose to 76 mm. of mercury and did not fall again to the base line of 25 to 40 mm. of mercury for 20 minutes. The authors supposed that histamine with its rapid-acting effect and ergotamine with its slower-acting effect might, in combination, represent an effective oxytocic.

In 1930 Feldberg and Schilf<sup>10</sup> reviewed all of the available literature on histamine. They observed that the virgin uterus was especially sensitive to histamine and they quoted Dossena<sup>8</sup> regarding its fleeting effect on excised strips of human uterine muscle. Concerning the use of histamine during labor, Jäger's<sup>16,17</sup> studies were extensively cited. He injected histamine in a dose of 8 mg. both subcutaneously and by the intramuscular route. A contractile effect on the uterus could quickly be detected by abdominal palpation. After several minutes, powerful and frequent pains occurred which seemed, for a time, to hasten the birth process and to cause the uterus to become painful and of a ligneous consistency. However, in several cases, after about half an hour, the cervix seemed less dilated, and effacement appeared to have regressed with actual impediment of labor. Koch<sup>23</sup> said that with doses of 0.5 mg. to 1.0 mg. strong labor pains were produced for 5 to 8 minutes and seemed to hasten labor. He also observed that in the use of histamine in the postpartum period a relaxation effect followed the immediate contractile action. He interpreted this effect as a possible fatigue phenomenon. He actually observed severe atony in the postpartum period when histamine had been used during labor.

Feldberg and Schilf concluded that the use of histamine during labor and immediately after delivery was unsuitable for the following reasons: 1, doses of a high order (8 mg.) lead to unsatisfactory and potentially dangerous side effects; 2, prolonged tonic contractions of the uterus may occur; 3, the cervix in some cases not only does not dilate but may contract; 4, the short-lived contractile effects are followed by relaxation; 5, premature separation of the placenta might be induced.

The same authors, in their chapter on the intoxications of pregnancy mentioned that although most authorities did not accept an anaphylactic theory of premature separation of the placenta, Kämmerer<sup>19</sup> believed that at least some of the lesser symptoms of the toxemias of pregnancy are on an allergy-anaphylaxis (histamine) basis.

Küpper<sup>25</sup> in 1930 discussed the work of Koch and Jäger further. Koch said that he had used histamine as a styptic in cases of severe hemorrhage and that injections of 0.25 to 1.0 mg. of the drug had stopped postpartum bleeding. He further stated that the duration of action of histamine lasted from 10 to 24 hours in some cases. Jäger thought that doses up to 6.0 mg. were without effect but that a dose of 8.0 mg. administered by either the subcutaneous or intravenous route produces powerful effects lasting from 60 to 90 minutes. He referred to the side effects of the larger doses as remarkable and objectionable.

Danforth and Gorham<sup>7</sup> in 1937 reasoned that "since histamine is known to be a powerful oxytocic" determinations of the histaminase content of human placentas would be of interest. Accordingly, by the methods of Best and McHenry, histaminase determinations were made upon 84 human placentas. These investigators observed that an increased concentration of histaminase was to be found in the

placentas of women with inertia and sluggish labors. However, Danforth<sup>26</sup> in a later and more detailed publication stated that although the amount of histaminase in the placenta showed some correlation with the efficiency of uterine contractions, the evidence was not sufficient to warrant a definite conclusion. Among the data denying the hypothesis of a correlative relationship was the conclusion of Marcou<sup>27</sup> who found that the concentration of histamine in the blood declines steadily in the few days before labor and does not return to normal until after delivery, whereas, if histamine were an essential oxytocic and histaminase its essential inhibitor, the converse might be expected. Danforth further observed that it had not been possible to initiate premature labor in guinea pigs or in rabbits by the administration of histamine in physiologic doses. He concluded that it was most likely that the histaminase content of the placenta was in no way related to uterine contractions but could be thought of rather as an index of the amount of active, functioning parenchymatous tissue in the placenta.

Kapeller-Adler and Adler<sup>21</sup>, and Kapeller-Adler<sup>20</sup>, demonstrated that the histaminase reaction was negative on the serum of nonpregnant women but that in normal pregnancy serum, the histaminase reaction was found to be positive without exception, irrespective of the substrate used. It was observed that in toxemic patients there was considerable histaminuria, or histamine was present in the urine in small traces, or lacking altogether.

Ahlmark<sup>1</sup> (1944) in his classic work stated that histamine has a contractile effect upon the uterus (less pronounced during pregnancy) and that the human placenta contains a considerable amount of histaminase. He observed a considerable increase of enzyme (histaminase) activity during pregnancy

from about the seventh week after the last menstrual period. At about this time, the increase in enzyme activity is so great that it is possible to demonstrate the increase from one day to another. During the latter part of pregnancy, the enzyme activity attains about 500 to 1,000 times the normal value.

Koloszynski<sup>24</sup> (1945) found that there was clear evidence of specific histaminase activity in the last 6 months of pregnancy but no evidence of such specific activity in nonpregnant women. This author, however, found no inhibition of histaminase activity in preeclampsia as reported by Kapeller-Adler.

Hofbauer<sup>14</sup> in 1946 reviewed the evolution of the biologic concept of the cause of the late toxemias of pregnancy and discussed the literature on histaminase.

Page<sup>28</sup> has discussed a related topic and expressed the opinion that the histidinuria of pregnancy is due to an inhibition of or interference with the renal tubular mechanisms rather than the result of any hormonal inhibition of hepatic histidase by chorionic gonadotropin, as proposed by Kapeller-Adler.

Rose, Harkness and Forbes<sup>29</sup> confirmed Ahlmark's work regarding the increase in the concentration of plasma histaminase in pregnancy.

Editorial comment in the "Obstetrical and Gynecological Survey" in 1946 regarding the articles of Page and Koloszynski, referred to above, reviewed the implications of the relationship of histidine, histamine and histaminase metabolism in pregnancy. It was pointed out that the evidence for a histaminic cause for eclampsia was certainly inconclusive but that a theory of histamine intoxication in placental abruption was a somewhat more reasonable hypothesis. It was stated that histamine is a potent protoplasmic poison (Hueper and Ichikowski<sup>31</sup>);

that it exerts a powerful stimulating effect directly on the myometrium, and that this amine can produce profound shock and in animal experimentation can produce a good replica of abruptio placentae.

Cushny<sup>5</sup>, discussing histamine, said that the stomach, intestines and uterus contract powerfully and may pass into spasm in response to histamine and, as the effect is not counteracted by atropine, it probably arises from direct action on the muscle. The uterus, he said, is exceedingly sensitive to the presence of histamine.

Selye<sup>30</sup> reminded that the musculo-tropic actions of histamine are so marked that some of them serve as a basis for its bio-assay; that is, contraction of guinea-pig intestine or uterus *in vitro*.

Sollmann<sup>31</sup>, in the 1948 edition of his "Manual of Pharmacology," said that, clinically, a hypodermic injection of 0.33 mg. to 2 mg. of histamine produces prompt and powerful but brief stimulation of the parturient or postpartum uterus with spasmodic contraction beginning in 1 or 2 minutes and lasting for half an hour (Bourne and Burn<sup>4</sup>; and Jones and Barlow<sup>18</sup>.) He further stated that its use is not satisfactory as it causes undesirable side reactions—marked vasodilatation, rapid pulse, headache and violent vomiting. Sollman made the further reminder that the excised uterus of a woman is also stimulated (Kehrer<sup>22</sup>, Guggenheim<sup>12</sup>) as are the uteri of pregnant and nonpregnant cats, rabbits and guinea pigs (Barger and Dale<sup>2</sup>), but the uterus of the rat is relaxed (Fuehner<sup>11</sup>).

**Clinical Observations.** In the 5-year period ending April, 1948, approximately 4,600 patients have been seen on the service of one of us (B. T. H.) and approximately 70,000 intravenous injections of histamine have been given. In addition, some 30,000 subcu-

taneous injections of this drug have been administered and approximately 1,200 patients have been instructed in the technic of self-administration of the drug by hypodermic injection. Fifteen of these patients (12 of whom had multiple sclerosis) were pregnant while under our care.

The average age of our pregnant patients was 27 years and only 3 patients were past the age of 30 years. Six of the patients were primigravidas and 9 were multigravidas. Seven patients received subcutaneous injections of histamine daily throughout the entire period of gestation. Intravenous injections of this drug have been given in every month of the pregnancy, and in 2 cases the injections were given at least 3 times weekly throughout the entire third trimester to within 3 days of delivery. In 13 of the 14 cases in which the patients have thus far been delivered, there has been no tendency to premature labor, although labor occurred 2 weeks before the expected date in 1 case (Case 14). Twelve of these 14 patients have had their labor after the expected date of confinement. The greatest number of subcutaneous injections given was an estimated number of 270 to 5 of the 6 patients who said that daily injections were taken during the entire pregnancy. The greatest number of intravenous injections given to any patient was 48.

The maximal amount of histamine given was administered to a primigravida, aged 23 years, who had multiple sclerosis. This patient received 45 intravenous injections, each of which consisted of 2.75 mg. of histamine diphosphate (1.0 mg. of histamine base) during the third, fourth and fifth months of her pregnancy. The patient received approximately 140 mg. of histamine diphosphate during her pregnancy. The average total dose for each patient per pregnancy was about 50 mg. of histamine diphosphate. Four

patients in this series were delivered at the Mayo Clinic.

Only one event which might in any way be construed as representing an untoward effect on the pregnant uterus

occurred in the entire series. A primigravida (Case 11, Table 1), aged 29 years, had an episode of slight vaginal bleeding 12 hours after a subcutaneous injection of 0.137 mg. of histamine

TABLE 1.—DATA ON THE SUBCUTANEOUS AND INTRAVENOUS ADMINISTRATION OF HISTAMINE TO PREGNANT WOMEN

| Case | Age | Gravida | Para | Diagnosis                     | Administration of Histamine |                     |                      |                                    | Duration of labor, hr.           | Lactation        | Miscellaneous   |
|------|-----|---------|------|-------------------------------|-----------------------------|---------------------|----------------------|------------------------------------|----------------------------------|------------------|---|
|      |     |         |      |                               | Route                       | Period of pregnancy | Number of injections | Average dose per injection*, (mg.) | Total dose by each route†, (mg.) |                  |   |
| 1    | 23  | I       | 0    | Multiple sclerosis            | Intra-venous†               | 3rd, 4th, 5th mo.   | 45                   | 2.95                               | 123.7                            | 36½              | None  |
|      |     |         |      |                               | Subcutaneous                | Last 4 mo.          | 120                  | 0.137                              | 16.4                             |                  | Uterine inertia, grade 2.   |
| 2    | 17  | I       | 0    | Multiple sclerosis            | Intra-venous†               | Last 3 mo.          | 48                   | 1.83                               | 87.9                             | 10½              | Adequate 6 wk.  |
|      |     |         |      |                               |                             |                     |                      |                                    |                                  |                  | Histamine daily until 4 da. before delivery   |
| 3    | 23  | I       | 0    | Multiple sclerosis            | Intra-venous†               | Last 4 mo.          | 44                   | 1.83                               | 79.1                             | 12½              | Adequate  |
|      |     |         |      |                               |                             |                     |                      |                                    |                                  |                  | Histamine every other day until 3 da. before delivery                               |
| 4    | 23  | III     | II   | Multiple sclerosis            | Intra-venous†               | First 3 mo.         | 32                   | 0.87                               | 29.1                             | 2                | None  |
|      |     |         |      |                               | Subcutaneous                | 1st, 2nd, 9th mo.   | 24                   | 0.137                              | 3.2                              |                  | None  |
| 5    | 24  | II      | I    | Multiple sclerosis            | Intra-venous†               | 2nd, 3rd, 4th mo.   | 34                   | 0.97                               | 31.1                             | 3                | None  |
| 6    | 32  | V       | III  | Pseudo tumor of brain         | Intra-venous†               | 5th mo.             | 24                   | 2.2                                | 52.9                             | Cesarean section | None  |
| 7    | 33  | V       | IV   | Multiple sclerosis            | Intra-venous                | First 4 mo.         | 50½                  | 1.08                               | 50.0½                            |                  |   |
|      |     |         |      |                               | Intra-venous                | 4th, 5th, 6th mo.   | 34                   | 1.08                               | 34½                              | 12               | Adequate  |
| 8    | 31  | III     | II   | Multiple sclerosis            | Subcutaneous                | Entire pregnancy    | 248                  | 0.11                               | 27.0½                            |                  |   |
| 9    | 42  | I       | 0    | Multiple sclerosis            | Subcutaneous                | Entire pregnancy    | 200½                 | 0.137                              | 27.4½                            | 2                | Adequate 3 wk.  |
| 10   | 25  | II      | I    | Migraine and tension headache | Subcutaneous                | Entire pregnancy    | 270½                 | 0.11                               | 29.7½                            | 17               | Adequate  |
|      |     |         |      |                               |                             |                     |                      |                                    |                                  |                  | Histamine administered every day during pregnancy labor and postpartum              |
| 11   | 29  | I       | 0    | Multiple sclerosis            | Subcutaneous                | Entire pregnancy    | 270½                 | 0.137                              | 37½                              | 11               | None and at-tempt   |
|      |     |         |      |                               |                             |                     |                      |                                    |                                  |                  | Uterine bleeding after administration of histamine. Much of bleeding not mentioned. |
| 12   | 24  | II      | I    | Multiple sclerosis            | Subcutaneous                | Entire pregnancy    | 270½                 | 0.137                              | 37½                              | 11               | Adequate 14 wk.   |
| 13   | 24  | II      | I    | Multiple sclerosis            | Subcutaneous                | Entire pregnancy    | 270½                 | 0.137                              | 37½                              | 11               | Adequate  |
| 14   | 24  | I       | 0    | Multiple sclerosis            | Subcutaneous                | Entire pregnancy    | 270½                 | 0.137                              | 37½                              | 11               | Adequate  |
| 15   | 24  | V       | III  | Migraine and tension headache | Subcutaneous                | Entire pregnancy    | 270½                 | 0.137                              | 37½                              | 11               | Adequate  |

\* Dose stated in terms of histamine dihydrochloride.  
 † Intravenous and subcutaneous administration of histamine.  
 ‡ Patients in several of the series.  
 § Intravenous dose as number of ampoules.  
 ¶ Patients are followed when power was written.

diphosphate (0.05 mg. of histamine base). The month of the pregnancy in which this bleeding occurred is not known. Since this is one of the smaller amounts of histamine given to any patient in the group, the significance of this bleeding is questionable.

The data regarding these patients are summarized in Table 1. The average duration of labor was 12.6 hours for the primigravidas and 7.4 hours for the multigravidas. No postpartum bleeding occurred in this series. The one Caesarean section was done because of a previous Caesarean section. No significant conclusions regarding lactation may be made. However, information is available regarding 12 of the 14 women who have delivered. Four women were unable to nurse their infants; 1 woman did not attempt nursing; 6 women nursed their infants adequately and 1 woman was able to nurse her baby for a period of 3 weeks. It is an interesting, but certainly not statistically significant, sidelight that the 2 women who received intravenous injections of histamine at least 3 times per week throughout the entire third trimester to within 3 days of delivery and were then delivered under our care had bountiful supplies of milk. All of the babies thus far delivered have been normal.

One additional comment may be made regarding the women who received intravenous injections of histamine regularly throughout the third trimester. It was distinctly observed by the technicians and attending physicians that the histamine tolerance of these women, as indicated by their susceptibility to ordinary therapeutic doses of the drug and by the intensity of their histamine flush, was distinctly lowered very shortly after the termination of their pregnancy. The thought is thus advanced that the elevated concentration of histaminase of late pregnancy may well have inhibited the intensity of the cutaneous flush and

other systemic side effects of histamine in the terminal stages of pregnancy, for similar doses of histamine could not be tolerated in the immediate puerperium.

**Comment.** We wish to suggest on the basis of our experience that there is at least an apparent lack of a clinical oxytocic effect when the mentioned therapeutic doses of histamine diphosphate are administered by the subcutaneous or intravenous route or by both routes to pregnant women. Zeller<sup>33</sup> has calculated and suggested, on the basis of his data and Ahlmark's data, that one might expect approximately 30 mg. of histamine base per hour to be inactivated by the histaminase (di-amine oxidase) present in approximately 5,000 cc. of blood of a pregnant female near term, and, therefore, that the amount of histamine which we have administered might, on theoretical grounds, be regarded as a nonoxytocic dose. (The blood volume<sup>3</sup> of an average sized male [70 kg.] is about 6,300 cc.)

We offer no preferred explanation as to why the oxytocic effect described by so many authors and attested by abundant laboratory study did not occur. Our only purpose has been to express the physiologic point that these relatively small doses of histamine did not elicit, from our patients, a clinically measurable uterine response. However, a few of the possibilities which immediately present themselves to explain the theoretical discrepancies are: 1, that the elevated concentration of histaminase known to occur in pregnant women might be responsible for the inactivation of the injected histamine (see Zeller's calculation previously mentioned); 2, that the dose of histamine used was not adequate to provoke a clinically observable oxytocic response (the workers who administered histamine as an oxytocic used some doses of a much higher order than ours); 3, that the altered neurogenic response in the 12 patients in

this series who had multiple sclerosis may in some way, in these patients, have altered the predicted effect.

Summary. Various authors have stated that histamine has an oxytocic effect on women and female animals. We have had occasion to prescribe the administration of histamine diphosphate in relatively small doses by the intravenous or subcutaneous route to 15 pregnant women. In only one instance was there possibly an untoward effect: a primigravida, aged 29 years, had slight vaginal bleeding 12 hours after a small subcutaneous dose, 0.137 mg. This was one of the smallest doses of the drug administered in these cases. Postpartum bleeding did not occur in any of the cases. We can offer no explanation as to why the oxytocic effect described by many authors and attested by abundant laboratory study did not occur in any of the 15 cases in our series.

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# THE ABSORPTION, DISTRIBUTION, EXCRETION AND TOXICITY OF BACITRACIN IN MAN\* †

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SINCE the original description of bacitracin<sup>5</sup> by Johnson, Anker and Meleney, a number of articles have appeared in the literature regarding the characteristics of bacitracin, the pharmacology of bacitracin in animals and the clinical effectiveness of bacitracin in the treatment of clinical infections in man<sup>1-4,6,7,9-12</sup>. As the clinical results have in large part been covered in these publications, no attempt will be made in this report to analyze the clinical results of bacitracin therapy in the 152 patients treated by members of the staff of the Hospital of the University of Pennsylvania. However, the absorption, distribution, toxicity and excretion of commercial preparations of bacitracin were determined in a limited number of patients. An attempt was also made to determine the concentration of bacitracin attained in pleural, ascitic, cerebrospinal and pericardial fluids in respect to the concentration of bacitracin in the blood serum. Studies were also made to determine possible toxic effects on the liver, kidney, and the cellular elements of the blood.

**ABSORPTION.** The concentrations of bacitracin present in the blood serum 1, 2, 4 and 6 hours after an initial intramuscular injection of bacitracin were

determined in 33 patients. The dosages used varied between 16,000 and 60,000 units of bacitracin. The majority of the patients received 50,000 units of bacitracin intramuscularly every 6 hours. Following a single intramuscular injection of 50,000 units of bacitracin the highest concentration of bacitracin in the serum was usually found 2 hours after the injection. At this interval of time the concentration was usually in the neighborhood of 0.3 units of bacitracin per cc. of serum, although concentrations as high as 1.0 unit and as low as 0.006 units per cc. of serum were observed. Six hours after the injection the average concentration of bacitracin was 0.03 units per cc. of serum with variations between 0.004 and 0.46 units per cc. of serum. After repeated injections of 50,000 units of bacitracin at 6 hour intervals for several days, bacitracin levels, ranging between 1 and 3 units per cc. of serum were frequently found. (See also Tables 1 and 2 and Figs. 1 and 2.) The method of determining the concentration of bacitracin in body fluids was devised by Miss Balbina A. Johnson. No correction was made for the partial inhibition of bacitracin by serum as described by Scudi<sup>11</sup>.

\* The work described in this paper was done under a contract between the Department of the Army and the University of Pennsylvania and was reported to the Subcommittee on Chemotherapeutic and other Agents of the National Research Council on November 22, 1948.

† The Bacitracin was kindly supplied to us by the Commercial Solvents Corporation.



TABLE 1. CONCENTRATION OF BACITRACIN IN BLOOD SERUM AND ASCITIC FLUID FOLLOWING A SINGLE INTRAMUSCULAR INJECTION OF 49,000 UNITS IN 3 AVERAGE CASES

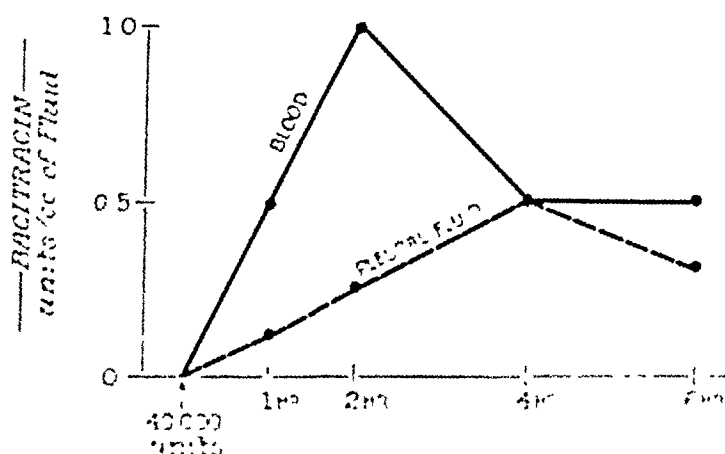
| Disease | Hepatic Carcinoma |               | Abdominal Carcinomatosis |               | Gastric Carcinoma |               |
|---------|-------------------|---------------|--------------------------|---------------|-------------------|---------------|
|         | Blood Serum       | Ascitic Fluid | Blood Serum              | Ascitic Fluid | Blood Serum       | Ascitic Fluid |
| 1 hr.   | 0.251             | 0.0018        | 0.016                    | 0.005         | ----              | 0.002         |
| 2 hr.   | 0.261             | 0.0291        | 0.0311                   | 0.004         | 0.006             | 0.008         |
| 4 hr.   | 0.841             | 0.0156        | 0.128                    | 0.064         | 0.125             | 0.062         |
| 6 hr.   | 0.46              | 0.064         | 0.064                    | 0.128         | 0.031             | 0.062         |

TABLE 2. CONCENTRATION OF BACITRACIN IN BLOOD SERUM AND SPINAL FLUID FOLLOWING THE INTRAMUSCULAR INJECTION OF 49,000 UNITS OF BACITRACIN IN A CASE OF BRAIN TUMOR

| Time After Injection | Blood Serum Level | Spinal Fluid Level |
|----------------------|-------------------|--------------------|
|                      | u/cc.             | u/cc.              |
| 1 hr.                | 0.12              | 0.0009             |
| 2 hr.                | 0.25              | 0.001              |
| 4 hr.                | 0.03              | 0.007              |
| 6 hr.                | 0.03              | 0.001              |

DISTRIBUTION. Bacitracin was readily distributed to pleural and ascitic fluids. Only traces of bacitracin were found in pericardial and cerebrospinal fluids. The concentrations of bacitracin found in blood and pleural fluid at intervals over a period of 6 hours following a single intramuscular injection of 40,000 units of bacitracin to a patient with

arteriosclerotic heart disease and myocardial infarction are shown graphically in Fig. 1. In this patient the pleural fluid concentration of bacitracin gradually increased until at the end of 4 hours it was equal to the then falling concentration of bacitracin in the blood serum. The concentrations of bacitracin in the blood serum and ascitic fluid following a single intramuscular injection of 49,000 units of bacitracin in a patient with abdominal carcinomatosis are shown in Fig. 2. The concentration of bacitracin in the ascitic fluid gradually increased until it was greater than the concentration of bacitracin in the serum 6 hours after the injection of the bacitracin. Table 1 shows the marked variations that occur in the bacitracin concentrations attained in ascitic fluid as compared to the serum



concentrations following single intramuscular injections of 50,000 units of bacitracin intramuscularly. The concentrations of bacitracin in the ascitic fluid of different patients may vary with the amount of ascitic fluid present and the disease process which produces the ascitic fluid. A patient with a brain tumor had only traces of bacitracin in the cerebrospinal fluid following 1 intramuscular injection of 50,000 units of bacitracin (Table 2). One hour after intramuscular injection of 49,000 units

of bacitracin, a patient with tuberculous pericarditis was found to have 0.005 units of bacitracin per cc. of pericardial fluid.

**EXCRETION.** The urinary excretion of systemically administered bacitracin during the first 24 hours of therapy was studied in 9 patients. The results are shown in Table 3. The total daily dosages varied between 80,000 and 260,000 units of bacitracin (20,000 to 65,000 units intramuscularly every 6 hours). The percentage of the total adminis-

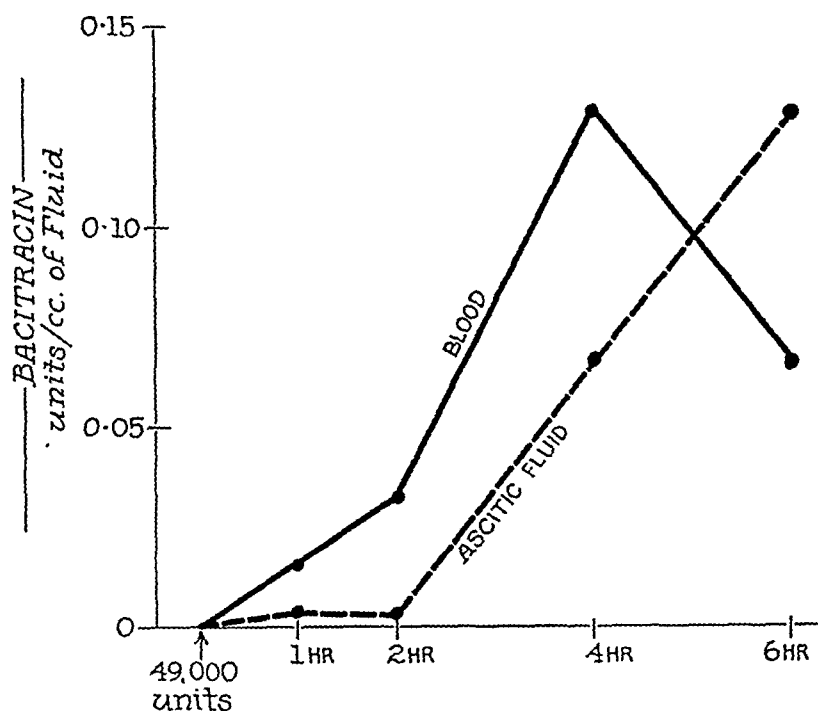


FIG. 2. Concentration of bacitracin in blood and ascitic fluid following a single intramuscular injection of 49,000 units in a patient with abdominal carcinomatosis.

TABLE 3. URINARY EXCRETION OF BACITRACIN, INITIAL 24 HOURS

| Patient | Bacitracin<br>Total Daily<br>Dosage<br>u | Daily<br>Urinary<br>Output<br>cc. | Daily Urinary<br>Bacitracin<br>Excretion<br>u | Percentage<br>Bacitracin<br>Excreted<br>% |
|---------|--|-----------------------------------|---|---|
| 1       | 260,000                                  | 2,500                             | 50,000  | 19.2                                      |
| 2       | 162,000                                  | 635                               | 15,325  | 9.4                                       |
| 3       | 196,000                                  | 1,425                             | 60,712  | 30.9                                      |
| 4       | 200,000                                  | 775                               | 42,660  | 21.3                                      |
| 5       | 216,000                                  | 3,060                             | 42,100  | 19.5                                      |
| 6       | 209,000                                  | 2,050                             | 60,200  | 28.7                                      |
| 7       | 196,000                                  | 1,575                             | 32,100  | 16.0                                      |
| 8       | 80,000                                   | 1,320                             | 20,240  | 25.3                                      |
| 9       | 200,000                                  | 875                               | 24,260  | 12.1                                      |

tered bacitracin excreted in 24 hours varied between 9.4 and 30.9%. It is apparent that considerable bacitracin is either retained or destroyed in the body. The 24 hour urine volumes of these patients varied between 635 cc. and 3,060 cc. of urine. In the data obtained there was no apparent correlation between the 24 hour urine volume and the percentage of the total administered bacitracin that appeared in the urine. In Patients 2 and 9 the 24 hour urinary excretion of bacitracin was again determined after several days of bacitracin therapy and the percent of the total daily dose of the antibiotic excreted was found to be 23.5% and 21.4% respectively.

**Toxicity.** The incidence of clinical evidences of bacitracin toxicity in 20 patients who received the antibiotic intramuscularly is shown in Table 4. Although the majority of these patients received approximately 50,000 units of bacitracin every 6 hours or a total daily dose of 200,000 units of bacitracin, several of the patients developed evidences of toxicity on a total daily dose as low as 50,000 units per day.

TABLE 4. CLINICAL EVIDENCES OF BACITRACIN TOXICITY IN 20 PATIENTS

|  | 7  |
|--|----|
| Local pain and induration (7)                            | 55 |
| Local petechiae (1)                                      | 5  |
| Skin rash (3)  | 15 |
| Nausea and, or, vomiting (5)                             | 25 |
| Appearance of albuminuria or increase in albuminuria (5) | 25 |
| ringing in ears (1)                                      | 5  |
| "Taste" in mouth (1)                                     | 5  |

The numbers in parentheses indicate the number of cases.

It is difficult to evaluate the degree of local pain experienced by a patient following an intramuscular injection. For the purpose of this evaluation, local pain and induration were considered as evidences of local toxicity only when the patient complained of pain or when

obvious induration was present for 24 hours after an intramuscular injection. Procaine solution (0.5%) was used as the diluent for all intramuscular injections. Pain immediately after injection of the procaine-bacitracin solution was minimal.

Petechiae of the skin in the area of an intramuscular injection were noted in 1 patient. Three patients developed an extensive macular skin rash. In 2 instances the rash disappeared during bacitracin therapy. The third patient developed the skin rash 7 days after bacitracin was discontinued. The patient, who developed the skin rash 7 days after discontinuation of bacitracin therapy, received no other chemotherapeutic or antibiotic agents before the rash appeared. The bacitracin was discontinued because of nausea and vomiting, which persisted until the rash appeared.

Nausea or nausea and vomiting were present in 25% of the 20 patients. In several patients it was necessary to discontinue bacitracin therapy because of persistent and severe nausea and vomiting. One patient with osteomyelitis of the spine, received bacitracin on 3 different occasions 3 to 5 weeks apart. There were no evidences of toxicity during the first period of therapy. During the second period of therapy he complained of nausea, ringing of the ears, and immediately after an injection, a peculiar taste in the mouth. The third time that bacitracin was administered the same symptoms were experienced and it was necessary to discontinue bacitracin after 3 days of therapy because of severe nausea and vomiting.

The appearance of albuminuria in patients previously free of albuminuria or an increase in the amount of albuminuria in patients who had albuminuria before bacitracin therapy was started, was noticed in 5 of the 20 patients.

**Blood Urea Nitrogen.** Blood urea nitro-

gen determinations were performed in 12 patients before and after bacitracin therapy (Table 5). Although the blood urea nitrogen levels increased in 7 instances and decreased in 5 instances, only in 4 instances were the increases significant. In 3 patients determinations of the phenolsulfonphthalein excretion before and after systemic bacitracin failed to show evidence of kidney damage in 2 of the patients, but did show some evidence of renal damage in the third patient. In this case the blood urea nitrogen rose from 13 to 31 and the 2 hour phenolsulfonphthalein excretion fell from 68 to 40% after the admin-

those changes in renal function observed following mercury bichloride, carbon tetrachloride and sulfanilamide poisoning. Five patients who received 23,000 units of bacitracin intravenously

TABLE 6. AVERAGE DIMINUTION OF RENAL FUNCTIONS AFTER THE SYSTEMIC ADMINISTRATION OF 196,000 TO 200,000 UNITS OF BACITRACIN DAILY FOR 4 TO 13 DAYS IN 5 PATIENTS

|   | %    |
|---|------|
| Glomerular filtration rate                | 45.8 |
| Renal plasma flow                         | 49.4 |
| Maximal tubular excretion                 | 61.4 |
| Maximal tubular reabsorption of phosphate | 36.2 |

TABLE 5. BLOOD UREA NITROGEN BEFORE AND AFTER SYSTEMIC BACITRACIN THERAPY IN 12 PATIENTS

| No. of Case | Days of Treatment | Total Units of Bacitracin | BUN Before Treatment<br>mg. % | BUN After Treatment<br>mg. % |
|-------------|-------------------|---------------------------|-------------------------------|------------------------------|
| 1           | 15                | 3,240,000                 | 15                            | 14                           |
| 2           | 24                | 2,640,000                 | 8                             | 10.5                         |
| 3           | 13                | 2,600,000                 | 17                            | 21                           |
| 4           | 10                | 1,960,000                 | 8                             | 14                           |
| 5           | 8                 | 1,760,000                 | 9                             | 33                           |
| 6           | 20                | 1,700,000                 | 8                             | 7                            |
| 7           | 7                 | 1,372,000                 | 10                            | 9                            |
| 8           | 18                | 1,368,000                 | 11                            | 13                           |
| 9           | 14                | 1,232,000                 | 15                            | 21                           |
| 10          | 7                 | 700,000                   | 8                             | 7                            |
| 11          | 8                 | 640,000                   | 13                            | 31                           |
| 12          | 1                 | 200,000                   | 21                            | 13                           |
|             |                   |                           | Average 12.1                  | 15.95                        |

istration of 80,000 units of bacitracin daily systemically for 6 days.

In 10 patients renal function tests were performed before and after bacitracin therapy. The 5 patients who received 196,000 to 200,000 units of bacitracin daily for from 4 to 13 days showed slight to very severe diminution in glomerular filtration rate, renal plasma flow, and maximal tubular excretion of para-aminohippuric acid (Table 6). The changes in renal function were similar to those observed in shock due to severe muscle trauma and severe hemorrhage; and similar to

for 1 hour, failed to show significant changes in the renal functions determined. Details of the renal function studies are being reported in a separate publication<sup>8</sup>.

**LIVER FUNCTION AND BLOOD CYTOLOGY.** Liver function studies were determined before and after the administration of systemic bacitracin to 4 patients. The patients received 50,000 units of bacitracin intramuscularly every 6 hours for from 4 to 10 days. No evidence of hepatic damage following the administration of bacitracin was found as judged by the van den Bergh reaction.

bromsulfalein retention, free and total blood cholesterol, cephalin flocculation, thymol turbidity or colloidal gold reaction. The only variation from normal noted was the change in the cephalin flocculation from zero to plus 2 in 1 patient. The average results of these observations before and after bacitracin are given in Table 7. Ten patients who received 50,000 units of bacitracin intramuscularly every 6 hours for periods of time varying from 3 to 19 days showed no evidence of blood cytology changes after the administration of bacitracin as judged by red blood cell counts and differential white blood cell counts before and after administration of bacitracin.

2. Bacitracin administered systemically is readily distributed to pleural and ascitic fluids.

3. Only traces of bacitracin are found in the cerebrospinal fluid.

4. Nine to 30.9% of the administered bacitracin was recovered in the urine in the initial 24 hour period of therapy.

5. Clinical evidences of the toxicity of the bacitracin preparations which we used for systemic administration were frequently observed. These included local pain and induration, local petechiae of the skin, extensive skin rash, nausea, vomiting, ringing in the ears, and a "taste" in the mouth.

6. Each of the 5 patients, who received from 196,000 to 200,000 units

TABLE 7. LIVER FUNCTION TESTS BEFORE AND AFTER SYSTEMIC BACITRACIN, AVERAGES IN 4 PATIENTS

|                         | Before                | After                 |
|-------------------------|-----------------------|-----------------------|
| Van den Bergh           | 0.14 mg. per 100 cc.  | 0.20 mg. per 100 cc.  |
| Bromsulfalein Retention |                       |                       |
| 5 minutes               | 2.82 %                | 1.2 %                 |
| 30 minutes              | 0.0 %                 | 0.0 %                 |
| Cholesterol             |                       |                       |
| Total                   | 151.5 mg. per 100 cc. | 138.2 mg. per 100 cc. |
| Free                    | 44.0 mg. per 100 cc.  | 35.3 mg. per 100 cc.  |

Cephalin flocculation, thymol turbidity, and colloidal gold tests negative except for a cephalin flocculation change of zero to 2+ in 1 patient.

It is evident that the bacitracin in the form supplied to us and in the dosages used is toxic in man. It is realized that the dosage of 200,000 units per day is larger than most investigators have used. The incidence of clinical evidences of toxic reactions may be high because of the large total daily dosage used in most of these patients, however the same types of toxic reactions were observed on a total daily dose as small as 50,000 units.

Conclusions. 1. Bacitracin blood serum concentrations after a single intramuscular injection of 50,000 units intramuscularly usually reaches a maximum approximately 2 hours after the injection and there is an appreciable blood bacitracin concentration in the serum 6 hours after the injection.

of bacitracin daily intramuscularly for periods of time varying from 4 to 13 days, showed moderate to severe diminution in glomerular filtration rate, renal plasma flow, maximal tubular excretion of para-aminohippuric acid, and maximal tubular reabsorption of phosphate.

7. No evidence of liver damage was indicated by the liver function studies employed in 4 patients who received 200,000 units of bacitracin intramuscularly daily for periods varying from 4 to 10 days.

8. No significant changes were noted in the red blood cell counts or the differential white cell counts in 10 patients who received large amounts of intramuscular bacitracin over periods of 5 to 19 days.

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# PROGRESS OF MEDICAL SCIENCE

## DERMATOLOGY AND SYPHILOLOGY

UNDER THE CHARGE OF

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## DRUG ERUPTIONS: A SURVEY OF RECENT LITERATURE

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THE literature on drug eruptions is so extensive that in this summary we shall aim to touch the high lights of our present knowledge and supply detail in those aspects of the problem which are either new and of practical value or in which we have been personally interested during the past two decades.

From the almost countless sources of information on drug eruptions, certain accessible studies are worthy of note. Among them are the monograph by Prince Morrow<sup>126</sup>, J. Jadassohn's early reports<sup>80</sup>, R. L. Mayer's<sup>119</sup> contribution to the Jadassohn Handbuch, the various papers by Abramowitz<sup>1a,d,2,3</sup>, Fox<sup>56</sup>, Wise<sup>201a</sup>, Wise and Abramowitz<sup>202</sup>, Wise and Sulzberger<sup>203a,b</sup>, Sulzberger's "Dermatologic Allergy"<sup>177</sup>, Sulzberger and Baer<sup>178</sup>, Longcope<sup>107</sup>, Brunsting<sup>30</sup>, Burgess<sup>31</sup>,

Kierland and Brunsting<sup>89</sup>, Wilson<sup>200b</sup>, Urbach and Gottlieb<sup>187</sup>, and Sherman<sup>167,168</sup>.

By drug eruption is meant a cutaneous or oral mucosal process incident to the administration of drugs, or their split products, which come in contact with the affected part by way of the general circulation. These eruptions may result from medicaments administered by ingestion, injection, inhalation or inunction. Absorption may occur from the skin, urinary bladder, conjunctiva, deep open wounds, vaginal, anal, oral and nasal mucosae, the pulmonary system, mother's milk and transplacentally. In this concept local application of medicaments producing eczematous contact eruptions are excluded. A number of factors are usually recognized as predisposing to these eruptions. Among them are

menses, menopause, pregnancy, other allergic processes, infections, functional states, organic disease, especially liver and cardiorenal, pigmentation or depigmentation (vitiligo), physical factors, sunlight, heat, cold, weather<sup>142</sup>, blood groups, vitamins, nutritional states, and personal status of the patient. For example, in our discussion of arsenical reactions<sup>172a,b</sup> we noted the following significant factors in the background of the eruptions (as well as other reactions) produced by this group of drugs: age, sex, race, number of treatments, dosage, type of syphilis, diet, nutritional state, vitamins, nervous reactions, seasons, pregnancy, toxemia of pregnancy, intercurrent infection, and technical elements. In the ensuing discussion only some of the above factors in the predisposing background of certain drug eruptions will be discussed.

Drug eruptions are not rare. While any of the thousands of drugs and chemicals used as medicines may be responsible for drug eruptions, such eruptions are less frequent than eruptions known to be produced by foods<sup>156</sup>. Among 100,000 consecutive general admissions to the University of Kansas Hospital, Sutton<sup>180a</sup> found that the ratio of drug eruptions to all illnesses was 1 to 2000 (0.05%). Of 4000 patients with various dermatoses observed in private practice, the incidence was 1 to 310 (0.32%). Abramowitz<sup>1c</sup> found the percentage among 56,634 admissions at the skin and cancer units of the New York Post-Graduate Hospital during the 5 years 1934-1938 to be 0.15% (1 of 65 patients with other dermatoses). Wise<sup>201a</sup> has summarized the incidence question as follows:

"Important as drug eruptions are, in their relation to every phase of medical practice, their incidence, when compared with the incidence of skin diseases in general, is low; moreover, most of them are mild and of short

duration. While many disappear more or less promptly when the offending drug is stopped, a small proportion are of long duration and may coexist with serious impairment of health and curtailment of productive activities; in a still smaller proportion of patients, the prognosis may be quite grave and the disease may be fatal.

"When one reflects on the enormous quantities of hypnotic, sedative, analgesic, cathartic and other medicaments including vitamins, hormones, antibiotics, etc., consumed by the public day in and day out, without causing untoward manifestations except in isolated instances, it becomes evident that hypersensitivity is of relatively rare occurrence. In this connection, it is of interest to note that some textbooks state that eruptions from aspirin are 'common.' This led the author to ask several dermatologists of many years experience how many aspirin eruptions they had encountered; one said 'between 35 and 50,' the other said 'only one.' One of the older general practitioners in New York could recall only one instance, which happened to be fatal and was recorded in the literature; in my experience of 40 years, I have seen only 4 patients with aspirin eruptions. Such a disparity is hard to explain.

"On the other hand, a large number and variety of drugs are significantly prone to induce eruptions showing great variations with respect to clinical symptoms, course, complications, response to therapy, prognosis and so forth. This group comprises for the most part, the iodides and bromides, the anti-treponemal arsenicals and bismuth, the various preparations of gold, the sulfonamides and penicillins and atabrine (quinacrine hydrochloride). Some drugs, of which nirvanol, used in the treatment of chorea, is said to be an outstanding example, provoke eruptions in all recipients. Under circumstances in which one or another of this group of drugs is used by *mass-administration*, such as obtains in large hospital wards and clinics devoted to the treatment of venereal diseases, the incidence of drug eruptions is naturally disproportionately high, when compared with their incidence in polyclinics and in private practice. This is true, also, with respect to gold compounds used in arthritis and in lupus erythematosus; perhaps the most significant occurrence, in this connection, is the incidence of eruptions resulting from the mass-administration of atabrine to the armed forces in the Pacific and parts of the Mediterranean areas, for the prevention and treatment of malaria. But even with respect to atabrine reactions in general, Agress found an inci-



dence of less than one-twentieth of one per cent."

The importance of drug eruptions is not reflected in the incidence figures, since we have indicated that the incidence is generally low. Because these eruptions may resemble so many cutaneous diseases of other causation and because persistence in the administration of the particular drug involved might end in disaster<sup>116,153</sup>, a thorough knowledge of the diagnostic clinical features of the eruption produced by the various drugs should be clearly understood.

The characteristics of the eruptions of drug allergy have been summarized by Sulzberger<sup>177</sup> as follows:

1. Even very minute amounts of a drug which has been well tolerated for weeks, months, or years may suddenly produce severe eruptions.
2. Once such an eruption has occurred, it is likely to recur upon subsequent minute exposures to the offending drug or to a related drug.
3. As a rule, the cutaneous response is entirely different from that produced by the pharmacologic or toxicologic action of the drug.
4. Drugs with entirely different pharmacologic actions often produce identical eruptions; and the same drug is often capable of producing radically different manifestations in different individuals—or in the same individual at different times.
5. The amounts required to elicit eruptions are often much smaller than those necessary to produce pharmacologic or toxicologic effects.
6. Many drug eruptions occur only in certain predisposed individuals and, regardless of the deliberate increase in dosage, can never be made to appear in the majority of individuals.
7. The role of cumulative effects can usually be ruled out. As a general rule, drug eruptions can recur upon re-exposure to small amounts, even years after the last previous exposure . . . and even when the last demonstrable vestiges of the previously administered drug have been eliminated.
8. The marked specificity of drug sensitivity can often be demonstrated. Individuals sensitive to one drug are frequently found to show no demonstrable sensitivity to isomers

of that drug or to drugs with only slightly altered chemical constitution. But, just as has been demonstrated in sensitivity to living allergens, with drugs also, group specificity and cross reactions may be demonstrable.

9. The usual forms and the general phenomena found in other proven allergic . . . responses have their exact replicas in many recognized drug eruption. . . .

10. It has been shown experimentally that many of the substances producing drug eruptions are capable of sensitizing the skins of human beings and laboratory animals.

Drug eruptions are of various types ranging from simple erythema to the complex "fixed eruption". They may be produced by a variety of drugs (See list compiled by Sulzberger<sup>178</sup>). Convenient compilations of these eruptions are available<sup>150</sup>. The following data compiled by Sulzberger are to the point:

#### SOME COMMON DERMATOSES AND THEIR MOST FREQUENTLY CAUSAL DRUGS\*

1. Acneiform, furunculoid and erysipelas-like eruptions—bromides, iodides, oils, tars.
2. Eczematous eruptions, with erythema, papulation, vesiculation, weeping and scaling—quinine, procaine, other local anesthetics, ephedrine, mercurials, formalin, sulfonamides, penicillin, arsphenamines, atabrine.
3. Erythema multiforme-like eruptions—phenolphthalein, antipyrine, salicylates, barbiturates, other soporifics, sulfonamides, penicillin, etc.
4. Erythema nodosum-like eruptions—iodides, bromides, salicylates, sulfonamides.
5. "Fixed eruptions," i.e., fixed, circumscribed erythematous, edematous or bullous and polychromatic pigmented eruptions—phenolphthalein, antipyrine, phenacetin, barbiturates, salicylates, the arsphenamines, atabrine and other acridine and acriflavine derivatives, gold, sulfonamides (all so-called fixed eruptions have in common the fixed, circumscribed nature of the site of sensitivity and reaction, and thus all tend to recur *in situ*).

\* Based on Sulzberger, M. B.: *Dermatologic Allergy* (Springfield, Ill.; Charles C Thomas, 1940<sup>178</sup>).

6. Lichenoid and lichen planus-like eruptions—arsenic, arsphenamines, atabrine and other acridine and acriflavine derivatives, gold, amphetamine sulfate (atopic dermatitis-like eruptions?).
7. Pemphigoid and ulcerating and vegetating eruptions—bromides, iodides, sulfonamides.
8. Purpuric eruptions—iodides, arsphenamines, particularly sulfarsphenamine, carbamides (sedormid), barbiturates, balsams, sulfonamides, etc.
9. Scaly eruptions, purely erythematous or scarlatiniform and morbilliform; dermatitis exfoliativa—arsenicals, atabrine, belladonna, balsams, heavy metals, nirvanol, salicylates, sulfonamides.
10. Urticaria and angioneurotic edema—salicylates, barbiturates, sulfonamides, penicillin, belladonna, atropine, iodides, bromides, the opium group, arsenicals, penicillin, phenolphthalein, amphetamine sulfate.

#### DERMATOLOGIC CONDITIONS WHICH MAY SHOW PARTICULAR SUSCEPTIBILITY TO REACTIONS TO PARTICULAR DRUGS\*

1. Acne and acneform eruptions and furuncles are more susceptible\*\* to iodides, bromides, androgens, other steroid hormones (and certain foods—chocolate, shellfish, and so on).
2. Atopic conditions are more susceptible to salicylates.
3. Dermatitis herpetiformis is more susceptible to iodides, bromides, thyroid products (and certain foods including shellfish, sea fish, chocolate, nuts).
4. Hypertrichosis is more susceptible to androgenic substances.
5. Moniliasis and moniliids are more susceptible to iodides and bromides.
6. Purpuric and hemorrhagic conditions are more susceptible to barbiturates, arsenicals, gold salts, sulfonamides and salicylates.
7. Recurrent herpes simplex is more susceptible to iodides, bromides, salicylates (and certain foods—chocolate, shellfish, caviar, nuts).
8. Seborrheic conditions, intertrigo, infected and impetiginized eczematoid eruptions are more susceptible to antisyphilitic arsenicals, gold salts, penicillin and sulfonamides.

\* Sulzberger and Baer<sup>178</sup>.

\*\* More susceptible than a group of persons without these dermatologic changes or a history of these changes.

9. Urticarial eruptions are more susceptible to salicylates, iodides, bromides and a great variety of other drugs and of foods.

**Specificity of Drug Reactions Cutaneous or Other.** Although mention of specificity of drug reactions is made throughout this review, it might be emphasized here that the results of studies on the specificity of drug allergies are so variable that no generalizations are possible. Sherman<sup>167</sup> in his excellent review has presented the pertinent data on this matter as follows:

"This is best illustrated by sulfonamide sensitizations which have been most completely studied. Some patients sensitive to one sulfonamide drug have failed to react to any other members of the group. Other patients have reacted similarly to sulfadiazine, sulfathiazole and sulfapyridine but not to sulfanilamide. Still others have shown sensitivity to all drugs of the group. In some instances the sensitization was apparently to the para-aminophenyl radical and reactions were also obtained with sulfanilic acid, para-aminobenzoic acid and procaine. Park reported that 60 per cent of sulfonamide skin sensitizations were strictly specific for one drug while Sulzberger found only 10 per cent who failed to show cross reactions. Dowling, Hirsch and Lepper found that 69 per cent of sulfonamide sensitization reactions recurred if the same drug was used again but only 17 per cent if another drug of the group was substituted.

"In sensitizations to other types of drugs, instances of both strict specificity and group reactions have been reported. Cooke found that three aspirin-sensitive patients did not react to salicylic acid, benzoic acid, antipyrine, sodium acetate or methyl salicylate. Horsfall's patient, exquisitely sensitive to formaldehyde, did not react to other aldehydes, formic acid or methyl alcohol. Loveman reported a patient sensitive to alurate (allyl isopropyl barbituric acid) who did not react to barbituric acid or any of its other derivatives or to sedormid (allyl isopropylacetyl carbamide). On the other hand, Goodman described a case of a patient with procaine allergy who reacted to all the local anesthetics of the procaine group but not to those of the cocaine, quinoline or pyridine groups. Dawson and Gerbade reported a patient sensitive to quinine who reacted to seven related levorotatory compounds but not to quinidine, the dextroisomer

of quinine, or to any of the corresponding dextrorotatory compounds. Patients sensitive to arsphenamine usually react to all the related compounds containing trivalent arsenic but not to tryparsamide in which arsenic is pentavalent. However, there are several reports of arsphenamine sensitization in which the reactions to trial doses of tryparsamide have been the same as those to compounds of trivalent arsenic. In a given case of drug allergy only cautious trial will reveal whether other related drugs are tolerated."

### Pathogenesis of Drug Eruptions.

Eruptions and, or, other evidences of so-called idiosyncrasy to drugs have been an interest of physicians for many years, certainly as far back as the 18th century<sup>1b,10</sup>. In spite of this long concern and the present attention to this problem, the mechanism of drug eruption production is still obscure. In the past certain theories have been advanced to explain these eruptions. Among these are: "Saturation of the system" due to faulty elimination, particularly by the kidneys; "elective affinity" of certain drugs for anatomical elements, "irritation" of the skin due to the circulating drug, "modification of the sweat", chemical change of the drugs in the blood stream to products which led to certain eruptions, nerve origin; an endocrine stimulation with influences on the central and peripheral nervous system. The basis for our present understanding of the pathogenesis of drug eruptions was suggested only about 50 years ago when J. Jadassohn published his studies on idiosyncrasy as noted in drug eruptions. At present most writers<sup>1b,43,49,111,167,168,174,177,187,201a,203a,b</sup> believe that allergy is at the basis of most of these lesions. Other mechanisms for a smaller number of them are: cumulative effect (argyria); toxic effect (through liver?); non-allergic hypersusceptibility and biotropism (synergism). Sulzberger<sup>177</sup> has listed the following reasons for believing that drug eruptions are in general due to allergy.

1. Eruptions may be produced by *minute* amounts of drugs, sometimes long after the last medication—thus ruling out pharmacologic action and cumulative effect.
2. In most persons, regardless of large dosage, eruptions do not occur.
3. Eruptions usually recur from the *same* or *related* drug.
4. The clinical picture of a drug eruption is different from that due to pharmacologic action.
5. *Identical eruptions* may be produced by *unrelated* drugs.
6. One drug may produce different manifestations in different persons.
7. Some drugs may produce different manifestations in one person at different times.
8. Specificity of drug sensitivity can usually be demonstrated.
9. Some drugs, experimentally, sensitize skins of both humans and animals.
10. *Many manifestations that are produced by allergy to living microorganisms or to natural allergens can be reproduced by drugs:*
  - (a) Drugs, like other allergens, may exhibit incubation periods, spontaneous flare-ups and subsequent altered response to re-exposure.
  - (b) Can be ranged as to relative sensitizing capacity, viz.: non-pathogenic (cascara sagrada, yeasts, certain treponemes); facultative pathogens (phenolphthalein, monilia); obligatory pathogens (nirvanol, spirochaeta pallida, measles organism).
  - (c) Tend to produce characteristic pictures, e.g.: tubercle bacillus (tubercle); treponema pallidum (chancre); phenolphthalein (fixed eruption); arsphenamine (exfoliative dermatitis).
  - (d) Elicit variations in host susceptibility, e.g.: mouse (immune to syphilis); rabbits (immune to arsphenamine); all laboratory animals (immune to both gonorrhea and halogens).
  - (e) Produce changes which may persist for long periods.
  - (f) Exhibit spontaneous fluctuations.
  - (g) Are dependent upon environmental and dietary influences.
  - (h) Tend to select certain issues and sites.

On the other hand, Dragstedt<sup>49</sup> believes there is substantial reason to conclude that a variety of drug idiosyncrasies may depend on various non-allergic factors, and it seems probable that some drugs may produce both

allergic and non-allergic types of toxic reactions at the same time. There is merit in attempting to distinguish between reactions, and to that end he suggests the following provisional criteria:

An allergic basis seems to be indicated, 1. When the pattern of the toxic reaction is consistent with that of the allergic disorders produced by antigenic agents. This means that reactions characterized by urticaria, dermatitis, angioneurotic edema and asthma are probably allergic in character; that reactions characterized by jaundice, acute yellow atrophy of the liver and optic atrophy are probably not allergic, while granulocytopenia, anemia, thrombocytopenia and polyneuritis may well be one or the other. 2. When a priming or sensitizing administration of the drug appears to be a factor in the history, while a non-allergic basis seems to be indicated when either long-continued administration or the use of substantial doses appears of major importance. 3. When the untoward reactions are alleviated by epinephrine, diphenhydramine hydrochloride ("benadryl hydrochloride" N.N.R.) and similar agents, whose ameliorating effects are most reasonably interpreted on the basis of an anti-allergic effect. A non-allergic basis seems to be indicated for those reactions which are alleviated by ascorbic acid, folic acid, thiamine and other agents whose ameliorating effect is not reasonably credited to an anti-allergic effect.

**Immunology of Drug Eruptions.** The immunologic mechanisms of drug eruptions, and drug allergy in general, has received considerable attention. On the whole, while there are data to support various viewpoints and beliefs regarding the mechanisms involved, final demonstration of the exact *modus operandi* of drug sensitivity is far from certain. For example, although Longcope<sup>107</sup> has apparently demonstrated the probable mechanism involved in serum sickness, a corresponding mechanism has not been demonstrated for the urticarial reactions to penicillin which are clinically identical with serum reactions. The development of antibodies and positive intracutaneous and other types of tests in these cases

have been reported by some investigators and their existence denied by others<sup>117</sup>. At the Roosevelt Hospital Allergy Clinic in New York, Sherman<sup>167</sup> reports that neither the skin test nor passive transfer is a reliable index of penicillin sensitivity since small urticarial reactions to skin tests with penicillin may occur in non-sensitive individuals and the tests are often completely negative during or shortly after an urticarial reaction. Skin sensitizing antibodies were present in the serum of less than 10% of clinically sensitive patients and then in such low titres as to be of questionable significance. The antigen cannot be demonstrated in the circulating blood if the reaction occurs more than 24 hours after the last dose of penicillin even though there may be amounts of the drug adequate for antigenic activity still in the body during the reaction.

Although antibodies have been demonstrated to a few drugs (crystalloid non-protein substances), most of the persons with eruptions due to these products do not usually develop positive reactions to skin tests (intracutaneous) nor are antibodies demonstrable in the circulating blood. The usual methods of demonstrating antibodies do not seem to be of value in the case of drugs. Landsteiner's<sup>95a,b</sup> hapten theory has been invoked to explain this anomaly. He and others<sup>36,96</sup> suggest that slight local injury, sufficient to liberate tissue protein, may be caused by the drug. This protein assumes the character of an auxiliary antigen and can thus conjugate with the hapten "drug" forming a complete antigen. These protein drug conjugates have been demonstrated for certain drugs<sup>155a</sup>. However, when some of the protein conjugates<sup>77,193</sup> are used in experimental animals, the reaction is of the anaphylactoid type and does not resemble the effects of uncombined drugs in man. Sherman<sup>167</sup> and others

could not reproduce the high proportion of significant results obtained by Leftwich<sup>10</sup>, who used sera of patients receiving adequate doses of the sulfonamides (which presumably contained sulfonamide bound to protein) as antigens for intracutaneous tests of sensitivity to corresponding drugs. A control test consisted of serum from the same patients when not receiving the drug.

Karsner and Hanzlik<sup>11</sup> thought that reactions to drugs were anaphylactoid changes induced by capillary thrombosis, agglutination emboli or capillary toxicity.

The relationship of drug allergy and infection in drug eruptions, especially after organic arsenical indication has been the special interest of Stokes and his co-workers<sup>17,22,171</sup> for about 30 years. They conclude:

"1. The literature of the subject of arsphenamin dermatitis evidences a growing appreciation of the role of infections, local, focal and general, in the complex causal background of this condition.

2. A part of the influence of infection is probably exerted through the allergic mechanism of arsphenamin sensitization, and involves the conception of multiple balanced and summation effects, as suggested by Vaughan in general, by Harkavy and Hebard for infectious asthma and arthritis, and by the observations of Moore, Woo and Robinson on the reactivity of atopies to arsphenamin intradermally.

3. When the infection involves the skin, and also in antecedent or induced dermatitis from other causes, the local dermatitic focus acts as the excitant to a general flare-up following arsenical medication, through the vasodilation mechanism suggested by Auer, by Schlossberger and by Amalie.

4. Dermatophytic infections may apparently act as participants in a "balanced" or a "summation" allergic complex involving an arsenical extending the range and increasing the severity of the allergic dermatitic response to the drug (Block, trichophylin).

5. A dermatophytic focus may also conceivably serve, through the induction of local vasodilation, as the starting-point of an "arsenical" dermatitis.

6. Minute amounts of arsphenamin in

arsphenamin-sensitive persons may flare up and tend to generalize a local, apparently mycotic dermatitis.

7. The interaction of a drug and infection allergy is, perhaps, reversible, and may in some cases take the course of Milian's "activation" of the infection focus, with an exanthem of the toxic erythema type and a flare-up of the local focus in the case of bacterial infections, or an exacerbation of the localized dermatomycotic process and a "mycotid" in the case of a fungus infection.

8. Clinical cases illustrative of these possibilities and of the interplay of multiple allergic susceptibilities and infection in the background of dermatitis (including the arsenical type) are presented. The last case described apparently combines explosive dermatitic response to an arsenical, to bismuth, to goose feathers, to a mycotic infection and to bacterial protein (Coley's serum) in observations extending over four years.

9. In dealing with arsphenamin dermatitis with focal infective lesions, mycotic or bacterial, treatment should be directed, albeit with caution, at the focal as well as the general process."

**Diagnosis of Drug Eruptions.** The diagnosis of drug eruptions frequently poses a challenge. The clinician often has an intuitive feeling that an eruption of local or widespread distribution is caused by a drug, though positive history of drug ingestion often may be lacking. The following clinical data and procedures have been employed with varying degrees of benefit in the definitive diagnosis of eruptions due to medicaments: 1, *Suggestive clinical picture* (outlined above); 2, *History*. The information that a patient is taking certain drugs may be of decided value in diagnosis if the following items are observed: initial exposure followed by a variable incubation period and then a sudden outbreak, increasing in severity and with a variety of constitutional symptoms, especially if the drug is continued, all point to the possibility of the eruption being of medicinal causation. But we must not forget that the ingestion or administration of the medicament and the

eruption may be coincidental; 3, *Course*. Improvement on withdrawal of the drug and flare-up after re-exposure. Readministration may be a hazardous procedure, even ending fatally. On the other hand, certain eruptions (*e.g.*, bromide, iodide) may develop slowly and disappear long after the drug has been withdrawn. Similarly, the eruption may not appear until years later (arsenical keratoses and carcinoma). There may be polyvalent sensitivity and the eruption may be due to the drug readministered; 4, *Diagnostic aids*. *a*, Cutaneous allergic tests are of little value. They may even be dangerous and induce sensitization (*e.g.*, arsenical intradermal tests<sup>154</sup>, patch tests<sup>13a,15b,c</sup>), or severe reactions<sup>71,101</sup>. Furthermore the results may be falsely positive or negative. Passive transfer procedures are also unreliable; *b*, Chemical analysis of lesions, other tissues and body fluids may yield positive results, thus identifying the presence of a particular remedial agent, but the findings may be coincidental. Spectroscopic studies have the same limitations; *c*, *Histopathology*. This is certainly of value in the case of bromoderma and iododerma which produce a rather typical pathologic response (iodide or bromide granuloma). In other cases there may be no clue in the pathologic picture of drug versus other causation of the eruption (*e.g.*, lichen planus due to atabrine or arsenicals and lichen planus of idiopathic causation). Recently Rich<sup>152a,b</sup> and other pathologists<sup>59,102,125</sup> have maintained that certain histopathologic changes occurring in experimental protein sensitization are characteristic of the allergic reaction, and have made the diagnosis of drug allergy on pathologic grounds in the absence of immunologic evidence. These changes consist of widespread foci of parenchymatous and collagenous degeneration with monocytic in-

filtration and arterial lesions resembling those of periarteritis nodosa and rheumatic fever. Similar lesions have been found in patients dying during or after sulfonamide therapy and occasionally other types of therapeutic agents, without receiving any foreign protein injections. Suggestive as the findings are, their use as conclusive proof of drug allergy in the absence of corroborative clinical and immunologic evidence has been challenged<sup>92,162</sup>; 5, *Blood*. Blood cell examinations are important, since blood dyscrasias often complicate a variety of drug eruptions.

We shall now detail certain aspects of the eruptions produced by a limited variety of medicaments. First among these is the characteristic eruption usually called "fixed".

**Fixed Drug Eruptions.** In 1894 Louis Brocq introduced the term fixed to indicate an eruption in which the cutaneous manifestations appeared as round or oval apparently edematous plaques from the size of a coin to that of a palm, recurring on various parts of the body and accompanied by an itching or burning sensation. The patches were dusty red at their onset and showed definite borders. At times these lesions progressed to form bullae. Desquamation or crusting (after the bullous lesions) appeared as the eruption faded, leaving a pigmentation of variable shade and duration in the areas affected. A special feature of the eruption was its tendency to relapse and recurrence of the lesions in the same sites.

The first drug from which such a process was noted was antipyrine. Soon after introduction of this drug in 1885 one type of eruption observed after its use was peculiar in that it recurred at the previously affected areas of the skin whenever antipyrine was again ingested. There were but few presentations on this subject until 1918, when Abramowitz<sup>1a</sup>, who has done more than

any author to publicize and define the concept of fixed eruption, reported on 5 cases of erythema multiforme associated with cutaneous pigmentation. At about the same time Howard Fox<sup>50</sup> described an eruption which he took to be erythema perstans following ingestion of phenolphthalein. In 1922 Wise and Abramowitz<sup>202</sup> were able to determine that the changes in Abramowitz' original patients, as well as others subsequently observed, were in reality examples of phenolphthalein eruption. Since then a flood of papers on fixed eruptions has appeared. Among recent publications are those of Newman<sup>171</sup>, Wise and Sulzberger<sup>201a,b</sup>, Abramowitz<sup>1a,d</sup>, Knowles, Decker and Kandle<sup>97</sup>, Abramowitz and Noun<sup>2</sup>, Belote and Whitney (list of phenolphthalein-containing preparations)<sup>18</sup>, Abramowitz and Russo<sup>3</sup>, Pillsbury (sensitivity to tryparsamide at sites of pigmentation from silver arsphenamine)<sup>147</sup>, Chargin and Leifer (arsenicals)<sup>35</sup>, Arnold, Jr.<sup>8b</sup>, Dostrovski and Sagher (sulfonamides)<sup>47</sup>, Freeman (sulfonamides)<sup>58</sup>, Goldschlag (quiniline)<sup>66</sup>, and Goodman and Arthur<sup>67</sup>. Much of the material in this discussion is from the works of Abramowitz and his colleagues.

In reference to drug eruptions, the term fixed does not indicate that such lesions are permanent or lasting since the eruption is not expected to reappear if the cause is eliminated. There are usually no permanent sequelae except from secondary or unrelated causes. The term fixed has been established by usage for such eruptions, even though they may never recur, because the reaction site is fixed and the eruption is observed to appear in the previously affected area or areas should a recurrence develop. Histologically these lesions present the features of banal dermatoses of the urticarial erythematous or eczematous varieties. In cases with pigmentation

there are varying numbers of cells containing melanin in the subpapillary layer.

Many drugs are now known to be responsible for fixed eruptions. The following have been reported as having produced such lesions:

|   |                                   |
|---|-----------------------------------|
| Acetanilid  | Eucalyptus, oil of                |
| Acetylsalicylic acid  | Iodides                           |
| Acriflavine   | Ipecac (emetine)                  |
| Aminopyrine   | Ipomea                            |
| Antimony and potassium tartrate   | Icacen                            |
| Antipyrine  | Magnesium hydroxide (magnesia)    |
| Arsenicals (acetylarsan, arsphenamines, mapharsen, trisodarsen, tryparsamide) | Mercury                           |
| Barbiturates  | Phenolphthalein                   |
| Bismuth salts   | Quinidine                         |
| Cinchophen  | Quinine                           |
| Emetine   | Salicylates                       |
|   | Sulfanilamide and its derivatives |

Although most of the drugs responsible are of the synthetic organic type, there is no relationship between them chemically which could account for their ability to produce such similar eruptions. Furthermore, there are reports that fixed eruptions have occurred in patients as a result of vaccines, liquors (alcoholic<sup>131a,b</sup>), Karaya gum<sup>28</sup>, lentils<sup>186</sup>, and tomatoes<sup>42</sup>. Wohlstein<sup>207</sup> has noted them after physical exertion and psychic stress, and Gougerot<sup>68</sup> found them resulting from certain metabolites. Menstrual disturbances have also been responsible for some cases<sup>57</sup>. Although a particular drug may be responsible for fixed eruptions in a given patient, such lesions may occur independently. Thus Ehrmann<sup>53</sup> noted that at times one of his patients would develop an eruption from antipyrine whereas at other times it would occur without antipyrine medication. Wise<sup>201b</sup> had a patient who developed fixed lesions from phenolphthalein which reappeared after use of a barbiturate. Chargin's<sup>34a</sup> patient with fixed eruption from arsphenamine had a flare of the eruption after administration of phenolphthalein. Another patient reacted similarly to antipyrine and bismuth. In yet another<sup>34b</sup> a fixed

eruption produced by arsenicals flared up not only after arsenical but from use of phenolphthalein as well. Abramowitz and Russo<sup>3</sup> observed a patient with fixed lesions on the hands with a history that phenolphthalein, barbitol and magnesium hydroxide, a good example of polyvalent specific sensitivity, manifested clinically as fixed eruption.

The mechanism of the production of fixed eruptions is as yet unknown. Certain facts bearing on this phase of the problem are worth mentioning. Tonnel and Raviart<sup>184</sup>, as well as Mibelli<sup>124</sup>, have indicated that antipyrine may be present in bullous type of fixed lesions induced by this compound. Local application (by rubbing) at the site previously affected with antipyrine ointment has reproduced a recurrence<sup>7</sup>. There is no definite information regarding the question as to whether other drugs may be found in fixed eruptions produced by them. Abramowitz<sup>1d</sup> has been unable to find either phenolphthalein or its conjugate in an eruption from that drug. Sandler<sup>158</sup> stated that he had demonstrated phenolphthalein in the normal skin of a patient with a phenolphthalein fixed eruption by means of the usual scratch test technique; but neither he<sup>158</sup> nor Abramowitz<sup>1d</sup> could subsequently confirm this. On the other hand, Lowenfish<sup>112</sup> believed he had detected, by a cataphoretic method, phenolphthalein in the skin of a patient with phenolphthalein eruption on the hands. He obtained negative results on one of Abramowitz' patients.

On the whole, after surface application, intracutaneous and subcutaneous injection, the various drugs responsible for fixed eruptions could not be recovered and identified. Bernstein<sup>22</sup>, however, obtained positive patch tests with the offending drugs in the case of the eczematous type of eruption.

Transfer to normal subjects of sensi-

tivity to phenolphthalein and other drugs producing fixed eruption has yielded variable results. Kenedy<sup>87</sup> reported success in transferring phenolphthalein sensitivity to 2 normal persons, but Abramowitz<sup>1d</sup> could not verify this claim by his own experiments using the same technique, namely, having the patients take phenolphthalein before they were given an intracutaneous injection of phenolphthalein before they were given an intracutaneous injection of phenolphthalein-sensitized serum (Walzer method). Rosenthal<sup>155a</sup> did obtain positive endermic reactions to phenolphthalein in patients apparently sensitized to phenolphthalein by the previous injection of homologous or heterologous serum containing conjugated phenolphthalein. Jacobs and his co-workers<sup>79</sup> also were able to sensitize guinea pigs to phthalic-anhydride, one of the intermediates used in the preparation of phenolphthalein.

An interesting phase of this subject is the outcome of auto-transplants which indicate that the local hypersensitivity in these eruptions resides either in the epidermal layers or in the neurovascular structure of the cutis. Wise and Sulzberger<sup>203a</sup> transferred an affected area to a normal site and a normal area to the previously affected site. After complete healing, phenolphthalein was administered by mouth. Contrary to the results of Naegeli and his co-workers<sup>130</sup>, as well as those of Urbach and his co-workers<sup>188</sup>, Wise and Sulzberger<sup>203a</sup> found that the normal skin grafted on the previously affected area reacted in a typical manner with the production of a phenolphthalein lesion while the previously affected skin, now grafted on a heretofore normal site, remained unaffected. They interpreted this to indicate that the "shock site" of the sensitivity was dependent on the deeper structures (nerves and blood



cases of this process. Kierland<sup>84a</sup> analyzed his experience with 29 cases. Atabrine dermatitis and an associated aplastic anemia were reported by Drake and Moon<sup>70</sup>. Rosenthal<sup>155b</sup> made a study of the histopathology of atypical lichen planus. His material comprised 21 specimens from all phases of the process. Goldberg<sup>65</sup> described the unusual features of this dermatosis. Two cases of vesicular eczematoid type of drug eruption from atabrine were reported by Becker<sup>11</sup>. Bereston<sup>20</sup> analyzed observations on 200 cases of lichen and dermatitis. Lutterloh and Shallenberger<sup>113</sup> collected 8 cases of unusual pigmentation at uncommon sites presumably due to atabrine. Ochronosis-like pigmentation was observed by Sugar and Waddell<sup>176</sup>. A case of fatal exfoliative dermatitis and hepatitis was encountered by Agress<sup>4</sup>; Ginsberg and Shallenberger<sup>54</sup>, as well as Kierland and his associates<sup>90</sup>, noted fluorescence of nails of persons taking atabrine. Pfaff<sup>143</sup>, and Nisbet<sup>134</sup>, described the dermatologic aspects of dermatitis due to atabrine. Hyperkeratosis of the palms and soles due to this drug was reported by Paxton<sup>138</sup>. Cases of atypical lichenoid or atypical lichen planus were renewed by Alden and Frank<sup>5</sup>, by Holbrook<sup>76</sup>, and by Singh<sup>170</sup>, Bazemore *et al.*<sup>12</sup>, Wilson<sup>200a</sup>, and Waddell<sup>190</sup>. In a well documented discussion, Benedek<sup>19b</sup> attempted to prove that "Atypical Lichen Planus" was really a cutaneous manifestation of Vitamin A deficiency. In 1949 Schmitt<sup>160</sup>, one of the early students of the problem, reported on the present status of Quinacrine (atabrine) dermatitis. It is of interest that veterans have residual lesions and recurrences of eczematoid dermatitis which they acquired in the tropical areas during, or after the recent war. Affected individuals are increased risks in any occupation requiring exposure to heat, friction or chemicals.

**Sulfonamides.** While the sulfonamides have been a boon to the successful combatting of infections, the medical and lay public learned soon after their introduction into the practice of medicine that they were two-edged swords. These drugs are capable of interfering with the life and activity of bacteria and some viruses and at the same time they have potential toxic and allergic by-effects on nearly every organ of the host. While the cutaneous reactions are, of themselves, relatively less serious than those which involve the hematopoietic system (agranulocytosis, hemolytic anemia) and kidneys (obstruction by crystals), the cutaneous manifestations serve to remind the practitioner of more serious consequences which may be on the way or are actually present in subclinical form. While the exact number of fatalities from the sulfonamides is unknown, 200 such cases have been reported<sup>106</sup>. The proportion of fatal cases that are solely cutaneous is also unknown but in a report of fatal sulfonamide exfoliative dermatitis by Weinstein and Domm<sup>105</sup> autopsy failed to reveal any satisfactory cause of death. Furthermore, in the report on sulfonamide toxicity as a cause of death in New York City in 1941<sup>179</sup>, among 28 probable sulfonamide deaths, 3 cases of dermatitis in all probability died of the cutaneous involvement, 2 of these had generalized dermatitis which followed sulfathiazole therapy, and the 3rd succeeded upon the administration of sulfapyridine.

The literature on sulfonamide cutaneous reactions has been extensively reviewed. Bloom's paper<sup>25</sup> should be read in its entirety by the interested reader. Greenwood<sup>70</sup> classified the cutaneous reactions resulting from sulfonamides into 3 categories: 1, Direct toxic effects from overdosage or cumulative effects. Subsequent administration of small doses in such patients

after recovery may not lead to recurrence. 2, Purely allergic reactions: in such cases an incubation period, usually 7 days between the first and second dose, is required for the sensitization to become manifest. 3, Allergotoxic. In some cases it is possible that the earliest manifestations of the toxic type of eruption was a faint finely papular exanthem. On continuation of the drug there was spread of the eruption and it became scarlatiniform, morbilliform or maculopapular. No lymphadenopathy accompanies it. Allergic dermatitic symptoms appear early in the course of sulfonamide administration and usually are characterized by itching, sneezing, lachrymation, and dyspnea with edema of the lips, eyelids and face. These eruptions may be of various types (see below). Allergotoxic eruptions usually appear after 7 to 14 days of average dosage.

Light sensitivity after administration of sulfonamides was noted early in the sulfonamide period. We have discussed this phase briefly in our review on Light Sensitivity<sup>172c</sup>. This phenomenon is not necessarily associated with sensitivity to the drug, although in some cases there may be limitation of the dermatitis to the areas exposed to the sun<sup>37</sup>. According to Combes and Canizares<sup>40</sup>, however, sensitivity to sunrays is not common following sulfanilamide administration.

The constant sunshine of the Middle East and the presence of a considerable number of ambulant patients with venereal disease undergoing chemotherapy in an open-air hospital, recently gave R. G. Park and W. M. Platts (N.Z.M.C.)<sup>137</sup> unusual opportunities to observe cases of the light-sensitive type of sulfonamide dermatitis. During the 12 months from October, 1940, to September, 1941, 486 patients received sulfanilamide, of whom 21 developed eruptions (4.3%);

309 received sulfapyridine, with 6 cases of eruptions (1.9%). Of the 27 cases, 8 occurred during July, and 6 during August. As measured by the photo-electric cell, the intensity of visible light in this part of the Middle East in July is about 4 times that in January. Photosensitivity occurred from the 8th to the 10th day of administration. Two patients were found to be photosensitive 2 days after chemotherapy was stopped. It appears that patients given sulfonamides for more than 6 days are possible victims of sunlight eruptions. The commonest lesions are erythematous papules in a morbilliform or roseoliform pattern, becoming confluent. Itching varies from severe to slight and is absent in some cases. Less common lesions are edema, urticaria, vesiculation, pustulation and desquamation. Fever and malaise were present in 12 patients. Most rashes subsided in 2 to 4 days. In many cases the presence of melanin is a protection against sun eruptions. Three observations support this view: 1, about one-third of patients are subjects who sunburn easily; 2, the bronzed parts of the body tend to be affected less than the others; 3, no eruptions have ever been seen in Maoris, who comprised about 100 of the patients treated during the 12 months. The following parts are affected in order of severity: 1, parts exposed to the sun during chemotherapy; 2, parts exposed in the past; 3, pressure points, such as the great trochanters; and 4, least of all, parts always kept covered, such as the bathing-trunk area. Avoiding exposure to sunlight, 6 patients completed their course of chemotherapy, and 3 had further courses later without ill effects. In the milder cases, a rash is no indication for discontinuing the drug.

More recently Watkinson and Hillis<sup>132</sup> observed transient eruptions in 136 (34.6%) of 470 men at an R.A.F.

station who were given a 10 day course of sulfanilamide, 2 gm. daily, as prophylaxis for streptococcic infections. Most of the men were vaccinated against smallpox shortly before, during or after sulfanilamide administration, and appearance of the eruption coincided in all instances with development of the vaccination pustule. The role of photosensitization was indicated by the occurrence of lesions exclusively in areas exposed to light—head and neck, except for a small V-shaped area on the forehead shaded by the forage cap, arms and forearms unprotected by sleeves, and, in a few cases, a small band about the ankles. A few men who had been sunbathing had more extensive rashes. In most instances the lesions were erythematous macules or maculopapules, although in 4 cases vesiculation was observed. The rash faded within 1 week, leaving brown desquamating areas. In 23 cases the eruption was confluent and associated with conjunctivitis, fever and malaise, simulating measles. The 136 affected men were divided into 4 groups, on the basis of time of vaccination with relation to administration of the sulfonamide. The men in the 1st group, in whom vaccination pustules developed while the drug was being given, showed the highest incidence of eruptions (49.8%). Those in the 2nd group, in whom vaccination pustules developed 8 days after sulfanilamide therapy was discontinued, also showed a surprisingly high incidence of cutaneous reactions (26.3%). In the 3rd group of men, in whom vaccination reactions had subsided, 4 eruptions (4.6%) were noted. These occurred only in patients with unhealed vaccinations. No rashes were present in the 4th group of 71 men, in whom vaccination was not performed or was unsuccessful.

In none of the cases did the rash recur on further exposure to sunlight. Patch tests were negative in 30 cases,

indicating that the eruption was a transient photosensitivity rather than a true sulfonamide dermatitis. Possibly, the vaccination pustule acted as an inflammatory focus from which toxins were liberated by the sulfonamide, causing photosensitivity.

We have noted the production of light sensitivity following virus infection (*cf.* lymphogranuloma venereum<sup>171</sup> with and without ingestion of sulfonamides. This occurs often in the so-called virus pyogen sequence<sup>172d</sup>).

Many types of eruption may follow the use of sulfonamides. Among them are morbilliform<sup>161,185</sup>; scarlatiniform erythema multiforme<sup>44</sup>; erythema nodosum<sup>107</sup>; urticarial and angioneurotic edema<sup>47</sup>; purpura, varioliform<sup>57</sup>; vesicular<sup>182</sup>; bullous<sup>51a, 60, 84b, 104, 135, 165, 175, 183</sup>; pustular; follicular; fixed eruption<sup>39, 47, 58, 110, 123</sup>; psoriasiform<sup>144</sup>; exfoliative dermatitis<sup>51, 129, 170, 195</sup>; pemphigus foliaceus-like eruption<sup>107</sup>, and bacteriids<sup>33</sup>.

Most of these processes differ little from similar eruptions produced as a result of administration of other drugs. There are, however, certain features of some of them which deserve special mention. At the outset, it should be noted that any type of eruption may result from any of the sulfonamides, and once a patient has developed a reaction to one preparation it is unsafe to administer another. For example, Arnold<sup>8a</sup> pointed out that it is not safe to administer succinylsulfathiazole to patients known to be sensitive to sulfathiazole. Sometimes, however, one type may be responsible for the majority of cases of a particular eruption. Most of the erythema nodosum-like eruptions have followed the use of sulfathiazole, but it has occurred after sulfanilamide or sulfadiazine. Lofgren in this connection stated that in his 24 cases of this type of eruption, the provocation effect of sulfathiazole was established, it was probable with re-

gard to sulfanilamide and possible but not demonstrated with regard to other sulfonamides. The bullous eruptions are frequently serious and even fatal. They may in all respects resemble those produced by phenolphthalein. Benedek<sup>19a</sup> believes that cutaneous eruptions due to sulfonamides were of 2 forms from the standpoint of mechanism of production: 1, genuine drug eruption, and, 2, Milian's biotropic effect. The former was of morbilliform or bullous type, the latter was pompholyx in type.

The relative incidence of cutaneous reactions produced by the sulfonamides may vary from preparation to preparation and even different lots of the same preparation, more of the various sulfonamides may be considered entirely safe in this regard. The literature gives highly variable figures and at best they do not represent the actual incidence since statistics dealing with individuals receiving repeated courses of sulfonamides yield considerably higher figures. For example, Lyons and Balber<sup>114</sup> observed 53 patients (17 control and 36 patients) who had tolerated the first course of sulfathiazole (4 gm. followed by 1 gm. every 4 hours during a period on an average of 5 4/5 days); 19 (36%) developed severe fever reaction during the second course of the drug therapy given 2 to 20 days later. Note should be made that if a patient does react during early therapy, the result is usually mild but subsequent reaction is apt to be severe or less fatal. The cutaneous reaction may be associated with other serious by-effects, especially in the hematopoietic system. The route of administration for development of sensitization may be only by injection or even local administration for therapy or testing for sulfonamide hypersensitivity<sup>104,165,175</sup>. Note was made above regarding the question whether ingestion of one sulfonamide

sensitizes the patient to other sulfonamides. While the evidence on this point is not entirely clear nor very imposing, the trend is toward the occurrence of cross sensitization.

With these features in mind, the incidence of sulfonamide reaction may be better appreciated. Dowling and Lepper<sup>48</sup> noted among their 500 patients treated with sulfonamides the following incidence of dermatitis; fever and, or, conjunctivitis 2.4%; from sulfadiazine 2%. Long, summarizing the literature<sup>106</sup>, noted 5.2% of eruptions after sulfathiazole therapy; 2.2% after sulfanilamide, 2% following sulfapyridine and 1.3 from sulfadiazine. Park and Platts<sup>137</sup> found the incidence of eruptions following sulfanilamide to be 4.3%, but only 1.9% after sulfapyridine. Other estimates from various compounds range from a total of 3.7 to about 10%.

The presence of sulfonamides in tissues may be determined by a histochemical method developed by MacKee, Herrmann, Baer and Sulzberger<sup>115a,b</sup>. Full details are given in the original communications. It employs Ehrlich's Reagent (p-dimethylamino-benzaldehyde) and has proved satisfactory in numerous studies in the cutaneous penetration of sulfonamides, after their solution in penetrating vehicles and their external application to grossly intact human and animal skins.

The pathologic changes produced by sulfonamide allergy in man have been studied extensively. More and his colleagues<sup>125</sup> found that the lesions usually combined necrosis of the tissues with activity of the reticulo-endothelial system. The findings suggested that the lesions were always an expression of allergy. French<sup>59</sup> noted striking histopathologic changes in 76 autopsies and 2 additional specimens of skin taken for biopsy from patients apparently sensitized to sulfonamides. Char-

acteristic acidophilic histiocytes were present in focal and diffuse infiltrations in 17 organs. Significant vascular lesions were characterized by fibrinoid necrosis, endothelial edema, and proliferation. Lichtenstein and Fox<sup>102</sup> observed a patient with necrotizing arterial lesions resembling those of periarteritis nodosa and focal visceral necrosis following the administration of sulfathiazole. Although no specific pathologic picture of the cutaneous lesions was recorded, it is worthy of note that the fatal reaction in this case began with a vesicular eruption. Geeves<sup>62</sup> emphasizes the danger signal afforded by cutaneous lesions. In his 3 fatal cases of streptococcal infections coming to autopsy, 2 with generalized purpuric eruption showed severe fatty metamorphosis of the liver and moderate fibrinoid necrosis of the liver and mesenteric lymphnodes. In the third case without skin lesions there were no splenic nor lymphatic findings.

Keefer<sup>86</sup> has summarized the problem of sulfonamide eruptions as follows.

"Skin Reactions—Among the common untoward reactions to the sulfonamides are various skin eruptions. They are characterized by their pleomorphism, and are frequently accompanied by other signs of drugs intoxication or hypersensitivity. They vary in frequency with different drugs, and they are often widespread in distribution. The lesions cannot be inhibited by the administration of para-aminobenzoic acid. There is nothing distinctive about the eruptions, since they may be erythematous, morbilliform, urticarial or purpuric, and in some cases a generalized exfoliative dermatitis, with massive edema, appears. Lesions resembling erythema nodosum are most frequently seen following sulfathiazole therapy. One of the curious features of some of the cases of dermatitis, especially those following sulfanilamide, is the fact that the eruption develops after exposure to sunlight, or, at least, is made worse following such exposure.

"The skin eruptions occur at one of three periods following the administration of the drugs. The usual time is between seven and nine days after the drug is started, although the lesions may appear as early as the fourth

day. They may occur, however, as a prompt or accelerated reaction within 24 hours after the drug has been started, or as late as 2 to 6 weeks. When the skin eruptions are prompt or accelerated, they almost invariably occur in persons who have previously received the same or a closely related drug. For example, the usual story is that they received the same or a different sulfonamide at some time in the past, and that a reaction consequently followed within 7 to 14 days. This delayed reaction, which was self-limited in duration, disappeared following withdrawal of the drug. Then, after an interval varying from a few days to months or even several years, the same drug or a different one is given, with a prompt reaction. The prompt reactions may occur after single small doses, and they may be more extensive and serious than the previous reactions, since they are sometimes associated with exfoliative dermatitis or the signs of toxic hepatitis. Although these prompt or accelerated reactions occur oftener in patients who have had reactions following the first experience with the drug, they may appear in those who have previously had the drug without any noticeable reactions. Patients who have acquired sensitivity to sulfa-pyridine may react in a similar manner to sulfamethylthiazole or sulfapyridine, but not to sulfanilamide, and patients who are sensitive to the esters of para-aminobenzoic acid (procaine hydrochloride) may be sensitive to sulfanilamide (para-aminobenzoic sulfonamide). It is plain, then, that the hypersensitivity to the drug may be specific, and that the reactions may follow the exhibition of a closely related drug. This suggests that there is a common substance in the various drugs to which some patients become sensitive.

"In most cases, the prompt hypersensitive skin eruptions are accompanied by fever, and in some, they may be associated with such features as toxic hepatitis.

"Delayed skin eruptions occur commonly between the 7th and 9th day after the drug is started, and fever is associated with the eruption in about half the cases. The fever may subside within 2 to 7 days after the drug is withdrawn, but the skin eruptions may persist for several weeks or even longer. Other associated features are generalized edema, enlargement of the lymph nodes, leukocytosis (often reaching a count of 70,000 or 80,000), transient jaundice without anemia, and eosinophilia (20 to 55%). The delayed skin eruptions may also be a feature in the patients with neutropenia or in the cases of jaundice occurring as late as

the 6th week after the drug has been discontinued.

"Although many observers have not encountered serious reaction to the sulfonamides and others have advocated long continued oral administration (*e.g.*, 2 weeks after completion of treatment<sup>181a,b</sup> to prevent sensitization to these drugs the dermatologists of New York<sup>46</sup> found it necessary to adopt the following resolution:

'Whereas, Repeated administration of sulfonamides either internally or locally may sensitize an individual to these drugs and thereby preclude their future use in serious diseases, such as pneumonia; therefore, be it

'Resolved, That the Section on Dermatology and Syphilology go on record as strongly disapproving the indiscriminate use of sulfonamide drugs in relatively harmless diseases of the skin which can be satisfactorily treated by equally efficient drugs; and be it further

'Resolved, That the Section condemn the use of prepared dressing containing sulfonamide drugs which are sold promiscuously to the laity.'"

**Penicillin.** The literature on Penicillin reactions is already colossal. Fortunately Ethan Allan Brown<sup>29</sup> has performed a great task by reviewing this subject for the period 1943-48. This review is based on 308 papers and an additional 52 papers, in which sensitivity is mentioned, but neither defined nor described, published from March, 1943, to October, 1948. The reader is referred to this paper for the references to the reports cited here. The earliest report indicating cutaneous reaction was that of Keefer and his colleagues who found 14 instances of urticaria among their 500 patients. Lyons claimed urticaria as the commonest single complication occurring in 5.7% of 209 surgical cases (U. S. Army). He classified his patients into 2 groups: those who reacted to a particular batch with chills, headache, facial flushing, muscular cramps, nausea, vomiting, and those who reacted to any type of penicillin with fever, urticaria and transient azotemia. Duemling in 1946 summarized the results of treatment in 17,879 Naval patients treated with penicillin for 65

clinical conditions. Of these, 892 were patients with latent, early and neurosyphilis. Of the total group 10% sustained Herxheimer reactions, urticaria, pruritus and fever. Thomas (1948) in an experience of 10,000 cases, found urticaria to lead the list in respect to frequency of reaction type (2.5%). This occurred in 7 to 12 days after onset of therapy, and persisted 4 to 5 days regardless of the continuation or discontinuance of penicillin therapy. Usually the penicillin would be continued after onset of urticaria. Angioneurotic edema occurred after penicillin oil beeswax (2 cases in 804 treated). Erythematous papular and dermatitic reaction occurred in a number of patients. Bullous dermatitis occurred in 2 patients. Cormia and his co-workers encountered 0.5% reactions among 2000 soldiers given prolonged penicillin treatment. Urticaria and angioneurotic edema were among the reactions listed. They observed a syndrome resembling serum sickness, acute syncope with transient urticaria-like eruptions, erythematovesicular eruptions, dermatophytid-like reactions and erythema nodosum. Intradermal tests with 3 brands of penicillin gave partial results in 84, 65 and 23%, respectively. Some patients with severe reactions gave negative results. Among 116 control subjects there were also some positive reactions. Crystalline penicillin also caused some of the reactions. Numerous other reports showed a variable incidence of cutaneous reaction to penicillin, of various types and routes of administration. Peck and his associates found that among those who had had no previous penicillin, reactions occurred in 5%, but among those who had received previous treatment, the incidence rose to 25%. Males sustained more reactions than females. Skin tests (intradermal) were positive in variable percentage. There is a variety of types of cutaneous reactions.

Among those resulting from oral and parenteral injection are:

ORAL ROUTE:

*Stomatitis and glossitis.*

*Melanoglossia* (black tongue) (lozenges).

*Aphthous stomatitis.*

*Thrush.*

*Glossodynia and exfoliation of filaments of filiform papillae of tongue.*

*Varicelliform eruption.*

*Urticaria and angioneurotic edema.*

*Dermatitis.*

**LOCAL CONTACT WITH SKIN.** Not discussed here, but contact sensitization may occur after previous oral administration.

**INJECTION. *Urticaria:*** May occur shortly or days after injections are started or some time after treatment is concluded. (acute or delayed reaction). The intervals between treatment courses may be of importance. *Urticaria* may be due to concomitant treatment (e.g., penicillin and heparin). *Urticaria* is often sole reaction to penicillin but may be associated with other signs and symptoms of serum sickness. Reactions may be serious enough to cause discontinuance of therapy.

**Local Reaction:** Induration and sterile abscess at site of injection of penicillin in beeswax reported by various authors. *Celulitis* or *pseudocellulitis* have also been noted.

*Pruritus* without rash.

*Morbilliform eruption.*

*Bullous eruption.*

*Purpura.*

**Exfoliative Dermatitis:** These may be severe. Patient may be sensitized by contact and react by injection. Exfoliative dermatitis may be delayed reaction.

*Dermatophytosis-like reactions.*

*Activation of dermatophytic focus.*

*"Id" reaction.*

The most careful studies done by Cormia and Lewis elicited the relationships between sensitization to penicillin and pre-existing fungus disease. Following a series of 8 experiments, the authors concluded that many of the local and systemic reactions occurring during or after penicillin therapy were the result of a previous sensitization by a dermatophyte. In 45 children, aged 2 months to 6 years, who had never previously demonstrated fungus disease or received penicillin therapy, there was a nonspecific immediate reaction after intradermal tests with 1000 units of penicillin, with no delayed 48 hour reactions. In 17 patients, however, who presented active fungus disease, but had received no penicillin, immediate reactions occurred following intradermal tests with 41% of the subjects, developing the 48 hour

tuberculin type of reaction. Of 8 guinea pigs, 5 developed papular lesions following the 2nd intradermal injection of penicillin given 28 days following the initial injection. In these 5 animals, the injection sites of the positive reactions were not flared up by intravenous injection of penicillin. There was no anaphylactic shock. Four of the 5 animals gave positive reactions to intradermal trichophyton injections. Five guinea pigs given weekly intradermal injections of trichophyton for 4 injections, followed a week later by intradermal injections of penicillin, did not develop sensitivities to either trichophyton or penicillin. A trichophyton gypsum infection induced in 6 guinea pigs resulted in positive intradermal reactions to penicillin in 3. In 7 rabbits with trichophyton purpureum infection of the skin, 5 developed positive reactions to penicillin.

In a later paper, Cormia, Lewis and Hopper evaluated the relationship between sensitization to penicillin and sensitization induced by superficial fungus disease by the Schultz-Dale test, using guinea pigs infected with *T. gypsum* or sensitized to penicillin. They demonstrated that in guinea pigs, anaphylactic sensitization to commercial sodium penicillin might be induced by a single injection given intradermally, or to crystalline penicillin sodium by a single intradermal, or 4 daily, intraperitoneal, injections. The guinea pigs could be sensitized anaphylactically to crystalline penicillin, in guinea pigs infected with *T. gypsum*. The authors feel that this positive reaction confirms the supposition that there is a common antigen in penicillin and the pathogenic fungi, which causes superficial fungus disease and that shock-like reactions in man are due to pre-existing sensitization by such pathogenic fungi.

*Aggravation of bacterids.*

Sensitization to penicillin may occur with different lots of the drug. Desensitization may be successful, according to Peck and associates, and O'Donovan and Klorfajn. A variety of drugs have been advocated in the treatment of penicillin cutaneous reactions. Intravenous nicotinic acid in doses of 35 mg. in 10 cc. of distilled water has been reported by Service for control of urticaria. The antihistaminic drugs, epinephrine, and similar preparations, have been used with variable results (Willcox, Pillsbury, et al.). Para-aminobenzoic acid has also been found of

value (Kampmeier; Gelfand). Procaine intravenously (1 gm. in 500 cc. of isotonic saline given in 2 hours) has been used by Van Root for urticaria. Vitamin K, Vitamin B and various other more specific measures have been used in therapy of these reactions.

Brown summarizes this subject as follows:

"At the present time information concerning penicillin reactions may be summarized as follows: 'The reactions occur most frequently in patients who have had several courses of penicillin. The continuation of penicillin treatment of a patient who has reacted with urticaria may or may not be tolerated. Skin tests are unreliable in predicting the occurrence of reactions and the anti-histaminic drugs may or may not control the reactions and permit continuation of penicillin therapy.' Pillsbury and his associates state that the urticaria reactions may be persistent and severe and may be accompanied by asthma and may be followed by ecchymoses and uterine bleeding. It is their opinion that the incidence of urticarial reactions is increasing as suggested by the fact that 1.8% of reactions occurred in the first 824 cases of syphilis treated at the University of Pennsylvania, whereas 12 cases have occurred in the last 200 patients treated between October 1945, and May 1946. Of 23 cases of urticaria treated with anti-histaminic drugs, 16 with Benadryl were relieved in 14; with no relief in 2 and 7 treated with PBZ showed relief in 2 and none in 5. In their opinion, penicillin must be halted as soon as a reaction occurs, unless there is immediate critical need of the drug. Antihistaminic agents should be given by mouth 3 times daily or slow intravenous injection in isotonic saline is advised if the reaction is severe. After subsidence of the urticaria or the accompanying symptoms, a test dose of another brand of penicillin (1,000 U.) may be given, while the anti-histaminic drug is continued by mouth. If there is no reaction in 6 hours, a second dose of 10,000-20,000 U. can be used followed by the full therapeutic dose if there is no reaction within 4 hours. The antihistaminic drugs should be continued and gradually reduced over a period of 2 to 3 days. No compounds prolonging the serum level of penicillin should be used during the period of trial administration. If re-administration is impossible and therapy is desirable, cau-

tious administration should be resumed after an interval of 4 or more weeks."

The available literature on streptomycin suggests that the same types and factors in drug sensitivity are being observed after use of this drug.

**Arsenicals.** The problem of arsenicals of various types producing cutaneous reactions has been covered in a vast literature. We have reviewed several aspects of arsenical eruptions in this Journal on two occasions. In our review of *The Trivalent Arsenicals in Syphilis*<sup>172a,b</sup> the types of eruptions and certain factors in their pathogenesis were discussed. In the review on *Tumors of the Skin*<sup>15d,e</sup> the arsenical keratoses and cancer were covered. In the present compilation we shall, therefore, mention some of the loose ends not touched upon in the previous presentation. Furthermore, the introduction of penicillin into syphilotherapy has materially lessened the incidence of these cutaneous reactions.

Arsenical jaundice has been given considerable attention lately. Most of the current literature has been reviewed, in connection with his own experience, by Ambrose King<sup>91</sup>. He concludes that the common prevalent type of post-arsphenamine jaundice is probably due to an infective agent introduced in the course of injections. It is preventable by careful technique in the sterilization of syringes and in the preparation of fluids for injection. The less common form of post-arsphenamine jaundice is possibly a sensitization phenomenon and due to individual idiosyncrasy. There is no known method of prevention, although some established cases may benefit from sulphur-containing amino-acids in adequate dosage. Subsequent arsenical therapy may be entirely well tolerated, but usually those in the group in which sensitization is suspected may require preliminary desensitization.



The 9th day erythema of Milian is usually regarded as harmless and is not an indication for cessation of arsenical therapy. Leifer<sup>99</sup>, however, has called attention to the danger of continued arsenotherapy in these cases of erythema of the 9th day. In a series of 14 instances of characteristic reaction continuation of arsenical after the initial reaction led to serious parenchymatous damage in the form of jaundice, agranulocytosis, with or without nephritis. It is interesting to note that 12 of the 14 patients subsequently tolerated penicillin therapy without incident.

**Barbiturates.** The literature on barbiturate reaction is voluminous. This is largely due to the numerous preparations belonging to this class of medicaments and to the alertness of the physician to the cutaneous manifestations produced by these drugs. A sample of recent literature affords ample illustration of the variety of cutaneous eruption as well as the demonstration that many types of barbiturate are responsible for them. Occasionally, however, one type of drug may lead to an excessive number of a particular reactions, *e.g.*, Purpura hemorrhagica<sup>122</sup>; from sedormid<sup>75,78\*</sup>. The same hemorrhagic cutaneous reaction may occur from phenobarbital in therapeutic doses (in a patient with myocardial infarction<sup>200a</sup>). Severe exfoliative dermatitis is occasionally encountered after these drugs. It may eventually in recovery<sup>127</sup>, or fatally<sup>164</sup>.

In general, the more frequently observed types of reaction to the barbiturates include a sensitization reaction, manifested chiefly by urticaria, pruritus and a toxic type such as morbilliform or scarlatiniform maculopapular erythema which in severe cases may lead to severe bullous (even hemorrhagic) process. Fixed drug eruptions are also occasionally observed<sup>109</sup>. Loveman pointed out in this

connection that cutaneous sensitivity to one barbiturate does not preclude sensitivity to other members of the group. Light sensitivity induced by the barbiturates is discussed in our review on Photodynamic Effects in Dermatology<sup>172c</sup>. Occasionally a granulomatous lesion may occur<sup>140</sup> and recently Berlin<sup>21</sup> has observed ectodermosis erosiva pluriorificialis due to phenobarbital. The observation that barbiturate given to the lactating mother may appear in human milk<sup>120</sup> has suggestive implications for the infant.

**Bromides and Iodides.** An interesting and controversial chapter in the problem of drug eruptions is that of the halogens (bromides and iodides). In spite of the obvious relationship of certain clinically specific cutaneous processes to iodide or bromide ingestion or administration, publicity of these usually occasional reactions has played a somewhat deterrent role in the universal consumption of goiter-preventing iodized salt. Although there is usually agreement that these preparations do produce eruptions or aggravate certain existing cutaneous processes, the point of departure is in assessing the magnitude of the problem. However, recently Gaul and Underwood<sup>61</sup> have presented evidence suggesting that iodized salt does not unfavorably affect the course of acne vulgaris, a finding reminiscent of Sutton's<sup>180b</sup> proposal to use iodized salt in the therapy of this disease. Without attempting to resolve the various viewpoints in this controversy, we present some of the recent reports of cutaneous reactions in patients receiving these halogens. The severe non-cutaneous reactions sometimes occurring with the cutaneous will not be detailed.

Bechet<sup>13b</sup> has covered the etiologic role of iodized table salt in iododerma and incidentally he has collected the available literature on many aspects of the iodide problem. He came to the

\* Incorrectly classed with the barbiturates since sedormid is allyl-isopropyl-acetyl-carbamide, a hypnotic. (H. B.)

following conclusions, dramatically opposite to those cited above:

Since 1924, iodized salt has been recommended indiscriminately to the public, which has been assured of its complete safety. As a result, it is being used by thousands as a tonic, without even the knowledge that it is useful in goiter, and in ignorance of the fact that severe iododermas and even death, have followed the administration of iodine in less than medicinal doses, among its users.

Fifteen deaths are cited from the literature, and 3 non-fatal cases of iododermas of the bullous type, seen during the past year alone in patients using iodized salt are briefly described for the first time.

The role of iodized salt in the etiology of acne in many patients is well recognized by dermatologists. Its relationship to the acneform iododermas has been proved by the fact that the lesions disappear on its elimination only, or with the administration of ordinary salt. Recurrences on again taking iodized salt have occurred. Its etiologic relationship in some cases of acne vulgaris is shown by failure of response to roentgenotherapy until its use is discontinued. On questioning such patients, a history of the ingestion of iodized salt for long periods, was elicited, and they showed no improvement with roentgenotherapy. *All improved rapidly after discontinuing iodized salt, and the administration of sodium chloride by mouth or intravenously.* Acneform iododermas occurred in 18 cases, and the results from Roentgen-ray therapy were equally unsatisfactory *until the iodized salt was stopped and sodium chloride given.*

In a recent report Ehrich and Seifter<sup>52</sup> described a fatal case of thrombotic thrombopenic purpura resultant from kelpidine, a commercial reducing agent containing kelp and

iodine. These investigators suggest that the purpura was caused by an antigen antibody reaction involving cells of the thrombocytic series. The involved cells agglutinated or disintegrated and occluded many capillaries; as a result the blood was depleted of thrombocytes and thrombopenic purpura ensued. Purpura following iodine therapy is rarely observed and the specific type described by Ehrich and Seifter is unique.

**Eruptions From Miscellaneous Drugs.** *Chloral Hydrate.* It is possible to find a person sensitive to practically every drug. For this reason it would be a futile task to list all the reports dealing with individual examples of reactions to this or that preparation. However, we shall mention certain recent reports. Baer and Sulzberger<sup>10</sup> have observed an instance of eczematous dermatitis due to chloral hydrate following both oral and topical application. This is a significant finding since dermatologists and others are prone to consider chloral hydrate a safe and satisfactory sedative especially for patients suffering from barbiturate or bromide eruptions. The distribution of the reaction in Baer and Sulzberger's case resembled that of hematogenous eruptions following the use of the sulfonamides (scalp, face, neck, hands and forearms).

*Liver Extract.* The parenteral administration of liver extract has been reported infrequently. Jones<sup>82</sup> was able to collect 16 reports of reactions in the Quarterly Index Medicus to 1939. Only 6 of these were in the American literature. The reported reactions include mainly skin and pulmonary manifestations. Urticaria was the most frequently recorded cutaneous type. One patient with erythema nodosum was in this series. Jones, personally, had 2 patients with allergic reactions to this preparation, one exhibiting urticaria and the other anaphylactoid phe-

nomena. The sensitivity to liver is said to disappear after a time and desensitization is reported as possible. Administration of liver internally is also possible. We have observed one patient who developed urticaria only after liver extract of hog origin. Beef liver preparations were innocuous. The reactions in this case occurred after either parenteral or oral use of the preparations.

*Trimethadione (Tridione).* This preparation, recently introduced for the therapy of petit mal and related disorders, has been found to produce certain toxic phenomena among which are cutaneous lesions. Acneform lesions have resulted on occasion following its use. Shaffer and Morris<sup>166</sup> have reported severe erythema multiforme of the pluriorificial type (Stevens-Johnson Syndrome) resulting in blindness in a white boy aged 6½. Among other treatment he had received trimethadione in dosage of 0.3 gm. twice a day for about 16 days. (During this period 6 doses of 0.5 to 1 cc. of polyvalent anterior pituitary extract were also administered.) Three days before the last dosages of trimethadione were taken a red spot developed at the site on the buttock of an injection of the pituitary extract. However, on this date another injection of this product in the other buttock did not lead to a local lesion at this site. The following day bullae had developed about the lips. On the day following the last trimethadione injection a generalized eruption accompanied by fever, severe cough and dyspnea resembling asthma had appeared. During a stormy course the process subsided but not without permanent damage to the eyes. Tests (including passive transfer) with pituitary extract and trimethadione gave negative results. Although there is strong suggestion that trimethadione was the offending substance in this case, there is no clear-cut proof of

this, since simultaneous administration of more than one preparation confounds the issue. Recently Leard and his co-workers<sup>97</sup> have reported on a patient with hepatitis, exfoliative dermatitis and abnormal bone marrow occurring during tridione therapy.

*Mesantoin.* Methylphenylethyl hydantoin (Mesantoin), which has proved to be useful as an anticonvulsant in epilepsy, may cause serious side effects, among which are reactions of the skin and changes in the blood. Although the eruptions are usually benign and respond quickly to cessation of treatment with the drug, it is possible for this complication to be of a serious nature.

Ruskin<sup>157</sup> has recently reported the results of one year's administration of methylphenylethyl hydantoin to a group of 26 institutionalized patients. He indicated that 1, the occurrence of toxic reactions did not necessarily increase proportionately with the dosage; 2, toxic reactions appeared to depend more on the patient than on the drug. Of the toxic reactions, the complaint of drowsiness was the most frequent, but was independent of the dosage or the concurrent administration of phenobarbital. Only 1 patient (3.8%) presented an eruption. This was scarlatiniform in nature and appeared when the patient received only 0.1 gm. daily. The lesions disappeared when treatment with the drug was discontinued and did not reappear when the patient was again receiving the drug. By starting, the second time, with a smaller dosage and raising the dosage slowly, it was eventually possible for the patient to receive 0.3 gm. daily.

Since the completion of the 1 year study of the original 26 patients, the drug has become more plentiful and more patients are gradually being added to the original group. In only one of these did a rash develop. Unfortunately, this bullous eruption did

not present the fairly innocuous picture the writer might have expected from his own past experience or the experience of others. The author, therefore, warns against the unbridled enthusiasm which often follows the development of a new fairly successful treatment for a condition which, in the past, has been so unresponsive.

*Hydantal* (5-phenyl-5-ethyl-3-methyl-hydantoin) another anticonvulsant for use in epilepsy produces eruptions in about 4.5% of cases in which it is administered in combination with phenobarbital<sup>180</sup>. The eruption usually appears within 2 weeks and may disappear within about 10 days when treatment with the drug is discontinued.

*Dilantin Sodium* (Phenytoin; sodium diphenyl hydantoinate). By now the hypertrophy of the gums produced by this anticonvulsant is well known. In addition this preparation may produce a variety of cutaneous reactions. For example, Finkelman and Arieff<sup>55</sup> found one patient with a scarlatiniform eruption with fever and 6 with "pruritus" as well as 17 cases of gingival hyperplasia among their 41 patients treated with phenytoin sodium according to the method of Merritt and Putnam.

*Nirvanol Eruptions*. Nirvanol (phenylethyl hydantoin), a preparation for treatment of chorea, known to the Europeans since 1916 and introduced to American physicians in 1930 by Ray and Cunningham<sup>161</sup>, always produces cutaneous symptoms accompanied by a definite symptom complex after it has been administered for a certain fixed time and in exact amounts. Madden<sup>116</sup> in 1932 made an extensive review of the literature on this drug and as a result of his personal experience found the symptoms to appear with clock-like precision. On the second or third day after the administration of nirvanol is begun, the choreic movements are greatly exaggerated. They

are soon followed by sedative effects. Fever generally develops from the 7th to the 9th day, reaches a maximum in 24 hours and subsides during the next day or so. If the drug is continued, the fever is prolonged. The eruption usually appears between the 9th and 12th days. The lesions appear at first on the covered parts of the body and appear on the face and in the more severe cases. It is usually morbilliform and may resemble one of the ciccate exanthemata. Stomatitis, bullous or ulcerative, has also been described. It is of short duration but may recur. The histopathology of the lesions is the same as found in any toxic erythema. The prognosis of nirvanol eruption is usually good.

*Dinitrophenol*. Although one rarely has occasion nowadays to use dinitrophenol in the therapy of obesity, this preparation was extremely troublesome more than a decade ago. Beinhauer<sup>17</sup>, for example, recorded the case of a patient who had developed urticaria following its use. Hitch and Schwartz<sup>74</sup> in 1936 observed a patient who had developed multiple and severe reactions including exfoliative dermatitis, cataracts and polyneuritis. In his comprehensive study, Simkins<sup>160</sup> noted that "skin rashes, which are common, no longer excite their quondam fear." Because development of cataracts is too high a price to pay for weight reduction, Simkins felt that the clinical use of dinitrophenol should be reserved for urgent indications only.

*Acetophenetidin*. Often regarded as dangerous, this drug has been championed recently by Cohen<sup>38</sup> who concluded that there is little or no evidence to justify the inclusion of this compound in the category of dangerous drugs. He does, however, include it in the list of some of the drugs which cause dermatoses (allergic). There is no specific type of eruption caused by acetophenetidin. The types of cuta-

neous manifestations noted in this review include exanthemata, urticaria (angioneurotic edema), flushing of the face, and petechiae.

*Mercurials.* The subject of mercurial eruptions has been reviewed thoroughly by Wright<sup>206</sup> and Billo<sup>23</sup>. These findings need not be repeated here, but the report of Gibbs, Shank and Pond<sup>63</sup> on the absorption of externally applied ammoniated mercury is a reminder of the frequently overlooked possibility of widespread eruption and other mercurial lesions resulting from the local application of this medicament.

*Bismuth Compounds.* The cutaneous reactions to bismuth compounds have been fully covered in Modern Clinical Syphilology<sup>173</sup>. While penicillin therapy has largely eliminated this complication from bismuth, the introduction of new bismuth preparations for oral use in various dermatoses leaves a possible fruitful source for such reactions. Bismuth pigmentation is still reported<sup>104</sup>.

*Antihistaminic Drugs.* The various antihistaminic drugs (such as Benadryl and Pyribenzamine) have as yet yielded but little cutaneous reaction. Although an occasional case of dermatitis medicamentosa occurs from their use, they are singularly infrequent<sup>54b,c, 72,101,149</sup>. The possible occurrence of granulocytopenia from one or another of these preparations<sup>24</sup> suggests necessary vigilance for cutaneous and other reactions. Rives and his colleagues<sup>153a</sup> have just reported a fatality from ingestion of Thénylene (Methapyrilene).

*Various Drugs.* A number of drugs have on occasion recently been reported as productive of eruptions. For example, alopecia has been noted following the use of the antispasmodic cyverine hydrochloride<sup>100</sup>; exfoliative dermatitis from diethylstilbestrol<sup>84a</sup>; eczematous eruption from Carter's Little Liver Pills (Podophyllin)<sup>41</sup>; toxic

erythema and exfoliative dermatitis resulting from the administration of sulfocyanates in the treatment of hypertension<sup>11</sup>; erythematous and morbilliform and purpuric eruptions due to ephedrine<sup>9</sup>; scarlatiniform eruption<sup>155</sup>; and exfoliative dermatitis<sup>128</sup> from codeine<sup>162</sup>; argyria has been fully discussed in the monograph by Hill and Pillsbury<sup>73</sup>. Recently Boersma and Baker<sup>26</sup> in a study of the distribution of silver deposits in a patient with argyria, observed that the membrane proposita of the large axillary sweat glands contained little silver in contrast to the dense concentrations of silver in the connective tissue surrounding the small sweat glands. This disposition of silver seemed to be directly related to the difference in concentration of elastic tissue in the connective tissues enveloping the two types of glands. The revival of interest in gold products because of their effectiveness in arthritis has led to an ever growing literature on the reactions to gold compounds. While there have been numerous reactions in other systems, the cutaneous phenomena have been summarized by Kierland<sup>88b</sup> as follows: Cutaneous reactions are many, varying from simple evanescent erythema and pruritus to protracted universal exfoliative dermatitis or erythroderma. Urticaria or erythema multiforme may be the sole evidence of toxicity, while pruritus, localized or generalized, alone may be the symptom. Morbilliform and scarlatiniform eruptions are seen which may subside promptly when use of the drug is discontinued or may progress to exfoliative dermatitis. Rarely, eruptions simulating those of pityriasis rosea and lichen planus may be seen. Metallic gold may be deposited in the skin and give rise to a condition known as chrysiasis or auriasis. This is manifested by a diffuse slate-colored darkening of the skin and usually appears late in the course

of treatment or even months after treatment with gold has been discontinued. Thiouracil eruptions have been evaluated by the Council on Pharmacy and Chemistry of the American Medical Association<sup>189</sup>. Among 5745 patients in the report, 189 (3.3%) presented the following eruptions: urticaria 64; papular rash 37; morbilliform rash 23; erythema 18; macular rash 17; acneiform rash 3; pruritus 3; edema of legs 1; and unspecified dermatitis 23. It should be pointed out that these cutaneous reactions to thiouracil were usually mild, but the occurrence of urticaria in such high proportion cannot be summarily dismissed (*cf.* sulfonamides). These reactions were independent of dosage.

*Chloroquine* [7-chloro-4 (4-diethylamino-1-methylbutylamino)]. Quinoline, an antimalarial drug produced lichen planus-like eruptions in 2 individuals<sup>9</sup>. In spite of the increased and widespread use of amphetamine sulphate (benzedrine) and its analogue dextroamphetamine sulphate (dextedrine) only 1 questionable case of dermatitis was found by Kauvar, Henschel and Ravin<sup>85</sup> after a thorough search of the literature. They described an additional case of their own from amphetamine sulphate. Patch and scratch tests with the drug yielded negative results.

*Aspirin* (acetyl salicylic acid). Increasing numbers of fatal reactions to this universally used preparation are appearing, but in proportion to the number of people exposed to this medicament the incidence of reactions is indeed small<sup>51,60,94</sup>. Most of the reactions are thought to be of an allergic nature. Urticaria and purpura are the most frequent cutaneous reactions. Angioneurotic edema comprised 19% of the patients with reactions in Prickman and Buchstein's<sup>147</sup> series of hypersensitization to aspirin.

**Treatment.** Withdrawing the offend-

ing drug is usually effective of cure of drug eruption in a reasonably short time. However, because of certain exceptions, notably the halogens (bromide and iodide) and the arsenicals, auxiliary methods of treatment are required. No attempt will be made to outline all the procedures, but some of the recent proposals in this connection will be mentioned briefly.

Although penicillin may not be the last word in syphilotherapy, it has removed the much feared cutaneous reactions incident to the arsenical treatment of this disease. Prior to the introduction of penicillin a number of procedures for reaction prevention were detailed by Stokes and Beerman<sup>172a,b</sup> and by Stokes, Beerman and Ingraham<sup>173</sup>. Among the substances mentioned were sugars, calcium salts, degradation products of protein including the amino acids and other materials for admixture with the arsphenamine solution. No conclusion had been reached as to their actual merit. Vitamin C has been studied particularly; we (Beerman, Pariser and Wammock<sup>16</sup>) believe that derivative of this vitamin may have merit at least in the less severe cases. Sodium thiosulfate is no longer considered potent and clinical syphilologists have discarded it in the past 10 years. Liver extract has also enjoyed a certain amount of more or less deserved popularity not only for reactions to the arsenicals but for reactions to other preparations such as the sulfonamides. Perner<sup>139</sup> believes that the action of whole liver extract in ameliorating the toxic effects of sulfonamides and diethylsilbesterol is through its high content of ascorbic acid. Nicotinamide, Vitamin K, thyroid extract and certain hygienic measures have also been employed.

"BAL." Despite the advances made in controlling arsenical reactions, the therapeutic and preventive armamentarium was at best only partially effec-

tive. As a by-product of successful intensive search for a substance that would serve as an antidote to the arsenical gases, it was found that 2, 3 -dimercaptopropanol (BAL; British anti-Lewisite), discovered by Peters and his British co-workers<sup>141</sup> in 1945, was also effective in the therapy of certain metal intoxications. The literature on this remarkable substance has grown to large proportions since security regulations regarding it were removed. The July 1946 issue of the *Journal of Clinical Investigation* was devoted entirely to various studies on BAL. Randall and Seeler<sup>148</sup> in 1948 compiled all the published material available to the time of their review. Since these sources are readily available we shall mention only those facts pertinent to the question of prevention and treatment of drug reactions. Although BAL has afforded some additional ideas as to the mechanism of heavy metal action, it has not clarified the *modus operandi* of drug eruptions. Furthermore, BAL is not entirely innocuous either from the local or the sensitization standpoints. In specific poisoning by metals, BAL has been found effective or of suggestive value in those caused by arsenic, mercury, gold, lead, cadmium, silver and certain miscellaneous metals: antimony, tellurium, copper, chromium, nickel, zinc, thallium, selenium and vanadium. Further study is necessary to determine the precise value of BAL in the case of many of the latter elements. Since BAL may increase the toxicity of certain metals, it should not be used indiscriminately. BAL is commercially available in a preparation containing peanut oil and benzyl benzoate which is suitable for intramuscular injection only.

In the eruptions due to arsenic, especially the organic arsenicals (arsphenamines, arsenoxides), BAL has proven itself to be of exceptional value both

in essential recovery as well as relief of symptoms. In severe cases, edema, fever and pruritus disappear or greatly decrease in 24 hours and complete recovery takes place within 2 weeks. However, some patients respond only partially and require additional courses of BAL. Some cases may completely fail to respond. Development of abscesses at the sites of injection are fairly frequent. Although others have demonstrated the efficacy of BAL in other complications of arsenotherapy, we cite as a typical experience the results of Carleton, Peters and Thompson<sup>32</sup>. They used BAL in 44 cases of arsenical dermatitis; 41 of these patients had the acute exfoliative type. Three cases ended fatally and in 4 more it was impossible to measure the progress numerically. In the remaining 37 cases the mean number of days between the first injection of BAL and healing or nearly complete healing was 21.5 days. Eight cases developed abscesses at the site of injection.

It was hoped that the antihistaminic drugs would be effective against drug reactions of the skin, but not only are they of limited value, but as previously stated, dermatitis may occur as a result of their administration.

Since Wile and others<sup>108,109</sup> used sodium chloride in the therapy of iodide or bromide eruptions several other procedures have been proposed in the treatment of these eruptions. Wohl and Robertson<sup>204</sup> found the desoxy-corticosterone acetate in conjunction with sodium chloride was effective in bromide intoxication (non-cutaneous). Bondurant and Campbell<sup>27</sup> had previously found that adrenal cortex when given in combination with sodium chloride was apparently of value in the excretion of bromide and bromide effects. They presumed that the adrenal cortex restores the normal physiologic level of chloride.

Martin, Fisher and Thompson<sup>118</sup> found that the acute toxicities of sulfanilamide, sulfathiazole and sulfapyridine were markedly reduced (without diminution of therapeutic effect) by the prophylactic use of physiologic detoxifying agents such as cysteine, amino-acetic acid, calcium glucuronate and ascorbic acid. McGinty and his

co-workers<sup>121</sup> found that nicotinic acid also relieved sulfanilamide reactions. This was advised on the basis of the similarity of certain aspects of sulfanilamide reactions to pellagra and radiation sickness. They began treatment with 50 mg. 3 times a day on the 4th day of sulfonamide administration.

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# OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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## THE MEDICATED EXTERNAL AUDITORY CANAL

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ALTHOUGH it has been variously estimated that otitis externa constitutes from 5 to 40% of all cases encountered in otologic practice in the United States<sup>5</sup>—the wide variation being due to sectional differences in temperature and humidity—renewed interest in infection of the external auditory canal is essentially a by-product of the war years. This situation is the result of the high incidence and widespread distribution of otitis externa among military personnel in humid tropical and subtropical regions. By virtue of its exposed position to the outside world, the external auditory canal is open to invasion by numerous microorganisms; here a moist milieu containing cellular detritus and cerumen often serves as an adequate culture medium for the growth of bacteria and fungi. While the causative agent of otitis externa can be any one of a variety of bacteria and fungi, it is quite probable that the role of the latter, whether as primary or secondary agents of infection, has been exaggerated.

**PHYSIOLOGY AND BACTERIOLOGY.** The normal human skin harbors an enormous number of bacteria, which ordinarily are harmless. According to Price<sup>12</sup>, these may be divided into a resident and a transient population, the former usually remaining fairly stable. However, some influences, particularly heat and moisture, cause con-

siderable changes in the number of bacteria found on normal skin. Sometimes pathogenic bacteria suddenly become members of the resident flora of the skin; they may then be extremely persistent and difficult to dislodge. Once a foothold is gained in skin already diseased, bacteria are responsible, in greater or less degree, for many diseases affecting the human skin.

In the opinion expressed by Pillsbury<sup>11</sup>, the problem of the management of bacterial infection of the skin cannot be dismissed simply by a discussion of the diseases produced, the bacteria concerned and the disadvantages of the various antibacterial agents now available, especially since these agents still have certain definite shortcomings. The management of the more difficult and more resistant cutaneous infections can be improved by a better understanding of the manner in which the skin resists and harbors bacteria and of some of the mechanisms by which bacteria produce harmful effects. Several factors apparently play a role in the remarkable protection afforded by the normal human skin against bacterial invasion. These factors, however, are imperfectly understood, and further basic study is necessary.

A factor of considerable importance is the pH of the skin. The surface of

the skin is enveloped by an "acid mantle," which exhibits pronounced defense against bacterial invasion. Determinations of the pH of the skin by a number of investigators reveal the following: 1, The seborrheic areas of the body are more alkaline than other parts of the skin's surface<sup>8</sup>; 2, the alkaline areas are less bactericidal than the rest of the skin, thus being predisposed to cutaneous infection; 3, in most cases of vesicular eczema there is a shift of the pH of the skin toward the alkaline side; 4, the highest degree of alkalinity is present in fissures associated with eczematous processes<sup>2</sup>; and, 5, moisture, maceration, dead horny tissue and relative alkalinity are 4 favorite conditions for the propagation of many forms of fungi. It has been asserted<sup>21</sup>: "The logical conclusion in managing many skin diseases is not to 'alkalinize' but rather to 'acidify'—at least as regards the skin's surface."

Measurement of the pH of the cutaneous surface of the external auditory canal was undertaken by Fabricant and Perlstein<sup>4</sup> in a series of 131 subjects (27 infants, 44 children and 60 adults) with no apparent lesions in their external auditory canals and either with no visible cerumen or with minimal amounts. A specially adapted glass electrode was employed in conjunction with the Coleman electrometer. In the group of adult male subjects, the pH range of the skin of the external auditory canal was found to be from 5.0 to 7.8, while in the group of adult females, the pH range was found to be from 5.0 to 7.6.

In the group of male infants, the pH range was determined to be from 5.6 to 7.6. In the group of female infants the pH ranged from 5.2 to 7.4. Male children, on the other hand, had a pH range from 6.0 to 7.9, whereas female children had a range in pH from 5.7 to 7.9. In general, there

was little difference in the pH range of male and female infants. The pH values fell chiefly within the acid range. Among children the tendency for acid pH values was not nearly as distinct as for other groups.

According to Hayes and Hall<sup>7</sup>, otogenic infections in the temperate zone are essentially of 2 types: a winter type due to gram-positive organisms, and a summer type due to gram-negative organisms. The primary infective agents in the latter group are *Pseudomonas aeruginosa*, (*B. pyocyaneus*), although in external otitis the infection is often mixed, with both grampositive and gramnegative organisms present. With the recent advance in chemotherapy and the use of antibiotics, otologists can demonstrate how they can eliminate the grampositive organisms and yet have the gramnegative ones flourish, their virulence unabated.

A study of Syverton<sup>19</sup>, and his associates reveals that the microbiologic flora of the external auditory canal in otitis externa, which in most cases is mixed, differs from the flora of the normal external auditory canal in the same clime by the inclusion of one or more pathogens. The causative agent of otitis externa can be any one of a variety of bacteria and fungi. Among these are *Ps. aeruginosa*, *K. ozaenae*, *Staph. aureus haemolyticus*, *Aspergillus*, and probably *Monilia tropicalis*. *Actinomyces* and *Proteus*. The role of fungi undoubtedly has been overemphasized in otitis externa, whether as primary or secondary agents of infection. Simon<sup>17</sup> found that in a series of 90 patients with otitis externa in a tropical climate there were only 21% in whom cultures yielded a fungus. In each one of the 90 cases it was possible to obtain a bacterial growth on culture, and it was believed that bacteria are the primary invaders in otitis externa.

**OTITIS EXTERNA.** The management of otitis externa still remains a complicated matter, first coming frequently to the attention of the dermatologist, then later to the otologist. The numerous therapeutic regimens are clear proof of the ineffectiveness of any single method of treatment. The introduction of a succession of new drugs has repeatedly seemed to solve the problem, but a painstaking study of various medicaments has invariably brought to light shortcomings which often counterbalanced any effectiveness these agents were thought to possess. Nevertheless, a number of medicaments occupy a useful place in the treatment of otitis externa, even though they do not promote consistent healing.

Dibromosalicylaldehyde has been described as being especially effective against gramnegative organisms, including pseudomonas, and also against fungi. In 71 patients with external otitis under Hayes<sup>7</sup> management, symptoms were relieved within 24 hours; in 30 the infection resolved in 1 week or less, and the remainder required 2 to 4 weeks' treatment. Wells<sup>20</sup> found the use of penicillin and glycerin wicks (500 units of penicillin per cc. of glycerin) satisfactory in relieving 60 individuals with acute otitis externa. Relief came on gradually and occurred within 24 hours in most instances. Senturia<sup>15a</sup> employed penicillin solutions and penicillin-sulfonamide mixtures in the treatment of 32 patients with otitis externa. Penicillin solution applied topically provided unsatisfactory therapeutic results in 10 of 11 cases diagnosed as acute diffuse, chronic eczematoid, or chronic desquamative external otitis. Rapid subsidence of pain and cellulitis and formation of well-localized abscesses occurred within 24 to 48 hours in 6 cases of circumscribed external otitis treated with intramuscular injections of pen-

icillin. While serving in the armed forces in India, Spence<sup>18</sup> treated a number of infected external auditory canals with 5% sulfanilamide ointment and found that pain generally subsided after the first treatment. Itching and all signs of irritation disappeared in nearly all patients when daily treatment was continued for a period of 7 to 12 days. Some patients required 3 to 4 weeks of therapy.

Pulaski and Matthews<sup>13</sup> declare that 5 patients with chronic otitis externa, due to susceptible organisms refractory to other agents, responded favorably to topical application of streptomycin, 5000 units per cc. On the basis of nearly 1000 cases of otitis externa observed in the army, Birrell<sup>3</sup> makes a number of recommendations. After thorough cleansing the meatus of all discharge, lotions are applied on wicks of ribbon gauze or painted on by means of wool-tipped wire probes. In acute edematous conditions he prefers 10% ichthammol in hypertonic sodium chloride solution, and 10% ichthammol in glycerin after 48 hours of treatment until there is no further exudation. At this point, 1% silver nitrate solution or an alcoholic (1%) solution of gentian violet (medicinal) should be used to harden the meatal skin. Goldstein<sup>6</sup> offers an original treatment for otitis externa. A solution is made by dissolving 1 chlorazene (chloramine, U.S.P.) tablet in 1 ounce of tepid water. The otologist flushes the auditory canal with this preparation on alternate days until the ear is dry. When this is achieved the canal is swabbed with metacresylacetate (cresatin) to which is added thymol in a concentration of 1%.

Furacin solution (5-nitro-2-furaldehyde semi-carbazone) has been reported by Anderson and Steele<sup>1</sup> to be effective against most of the organisms that are prominent in otitis externa. The fungicide employed was a

1% solution of thymol in metacresylacetate. Of the cases treated, 84.1% required no more than 3 visits before clinical well-being was established. The remaining patients responded somewhat more slowly, albeit they improved more rapidly than patients treated with other medicaments. McLaurin<sup>10</sup> describes his experiences with "Sulfamylon", a substance derived from benzylamine and differing from sulfanilamide in that a methylene group is inserted between the benzene ring and the 4-amino group. The preparation was found effective in a large number of patients with otitis externa and chronic otitis media. Reardon<sup>14</sup> maintains that "Iso-Par" ointment, which contains benzylamine salts of isoparaffinic acids, proved a specific medicament for otitis externa. It was found effective as fungicide, bactericide, anesthetic and stimulant to rapid healing.

**OTOMYCOSIS.** In 1844 Mayer first described a disease of the external auditory canal caused by a fungus known as otomycosis. Since then there have been many case reports describing symptoms and signs which are exceedingly diverse; the methods of treatment suggested are as numerous as the fungi isolated. It is believed by Wolf<sup>22</sup> that a factor of considerable importance in explaining the chaotic state of knowledge with respect to otomycosis is the failure to recognize that the disease is not an entity but rather a combination of different diseases caused by widely diverse organisms. In this connection, fungi are seldom isolated from the external auditory canal in pure culture but are frequently accompanied by bacteria. There is no certainty as to whether fungi are primary or secondary invaders. Furthermore, the fungi commonly isolated from infected auditory canals are, with few exceptions, not types whose pathogenicity is defi-

nately established. They are, for the most part, common organisms of the soil able to lead a saprophytic existence outside the body and can be isolated readily from dust or air. At least 53 different species of fungi have been reported to cause otomycosis. These belong to the Aspergillaceae, Mucoraceae, Actinomycetaceae, dermatophytes, yeast-like fungi, and a large variety of miscellaneous fungi imperfectae. The Aspergilli reputedly account for about 90% of the reported cases.

Otomycosis is of limited geographic occurrence, most frequent in tropical and subtropical climates. In the United States the reported incidence is greatest in Florida. Age, sex and race exert no significant influence. Water in the external auditory canals favors the growth and multiplication of fungi. Sharp and his associates<sup>16</sup> assert that the fungi associated with otomycosis ordinarily are saprophytes, such as occur on the normal skin. Excessive proliferation in the external auditory canal leads to a plug of thick, pulp-like exudate consisting largely of exfoliated epithelium and fungus mycelium. The external auditory canal does not favor fungus multiplication when it is normal, but only when its cutaneous physiology is altered.

Senturia and Wolf<sup>15b</sup> report *in vitro* experiments testing the action of sulfonamides on fungi isolated from cases of otomycosis. Ten strains of fungi were studied; 4 isolated from the auditory canals of patient with symptoms of otomycosis, and 6 from sources other than the ear but known to be capable of causing otomycosis. The effect of various sulfonamides was determined by sprinkling these agents in powder form onto the surface of agar plates immediately after inoculation. Of the sulfonamides tested—sulfathiazole, sulfadiazine, sulfaguanidine and sulfamerazine—only sulfanilamide was effec-

tive in inhibiting growth of the fungi under study. The experiments suggested that application of powdered sulfanilamide should be helpful in otomycosis unless the disease is caused by monila.

In the pre-sulfonamide-antibiotic era, McBurney and Searcy<sup>9</sup> made a study of the most effective solutions against aspergilli. Numerous substances were tried, the most effective being a thymol-cresatin-alcohol solution. Cresatin alone, thymol in alcohol, and tincture

of merthiolate were slightly less effective, and 2% salicylic acid in 95% alcohol was considerably less efficient. Their therapy included cleansing the external auditory canal thoroughly of debris, if necessary with hydrogen peroxide, and followed by mopping with a cotton applicator dipped in olive oil. A 2% solution of thymol in cresatin is then applied with a cotton swab. If there is considerable inflammation, drops of thymol, cresatin and olive oil solution may be used.

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# BOOK REVIEWS AND NOTICES

THE EPITOME OF ANDREAS VESALIUS. Translated from the Latin by L. R. LIND, Ph.D., Univ. of Kansas. With Anatomical Notes by C. W. ASLING, M.D., Ph.D., Univ. of California. Foreword by the Late LOGAN CLENDENING, M.D. Pp. 103; 20 ill. New York: Macmillan, 1949. Price, \$7.50.

Few would contest the view that Vesalius' *Fabrica* (1543) and Harvey's *De Motu Cordis* (1628) were the immortal works that initiated modern medicine—*De Motu* the junior by almost a century. Who, then, has not wondered why, in contrast to the many English translations of Harvey, none of the *Fabrica* or of Vesalius' condensation, the *Epitome*, made in the same year, had ever been published? Even the short *Epitome* has hitherto been available to non-Latinists only in a 1543 German and a unique Dutch translation of 1569, and only a few more than 20 copies of the Latin edition are in existence. But what a change have we seen in Vesaliana in the past decade! First, in 1943, Harvey Cushing's sumptuous Bio-Bibliography, and now, after more than 4 centuries, comes the first English translation of the *Epitome* and also the news that the lengthy *Fabrica* is being translated by Professor J. B. deC. Saunders, a leading authority on Vesalius and 16th century anatomical terminology.

Professor Lind's translation is a highly successful effort—liberally rendered, but accurate and aided by the use of modern phraseology—to produce a very readable text. Each of its 6 chapters is followed by a General Interpretation and Anatomical Notes by C. W. Asling that further facilitate understanding of the text. The 10 facsimile pages of the Latin text and 11 of the annotated woodcuts which complete the volume constitute an especially valuable addition to one's library in view of the great rarity of the original. Congratulations are in order to all who contributed to this model translation of a classic, not only for the intrinsic value and timeliness of the work but also for its attractive typography and general format.

E. K.

THE NEW YORK ACADEMY OF MEDICINE, ITS FIRST HUNDRED YEARS. By PHILIP VAN INGEN. Pp. 573; 46 ill. New York: Columbia Univ. Press, 1949. Price, \$10.00.

WITHOUT any question or doubt, this history, completed in the Academy's centennial year, will stand as the authoritative record of a famous institution whose influence extends far beyond its native city. Dr. Van Ingen has extricated from a large mass of often disconnected material all the events which have contributed to the Academy's growth and has set them down, year by year, in a largely disconnected detail. Little could have escaped his meticulous care. As a source of information, the book's value is permanent; we doubt, however, if it will attract many readers. To them we suggest that a start be made with the first few pages and the last chapter of comparisons and prospects, and then, if still interested, that they select special topics from the copious index.

E. K.

## NEW BOOKS

*Trends in Medical Education.* Edited by MAHLON ASHFORD, M.D. The New York Academy of Medicine, Institute on Medical Education, 1947. Pp. 330. New York: Commonwealth Fund, 1949. Price, \$3.00.

THE 6 chapters represent the 6 conferences held at an "Institute" conducted in connection with the centenary observance of the Academy. They present sound individual views on a subject of obvious importance to the nation's health.

*Economic and Social Council Commission on Narcotic Drugs.* By UNITED NATIONS, 1948. Summary of Annual Reports of Governments for 1946. Pp. 112. New York: Columbia Univ. Press, 1949. Price, \$1.00.

## NEW EDITIONS

✓ *Clinical Chemistry in Practical Medicine.* By C. P. STEWART, Ph.D. (Edin.) and D. M. DUNLOP, M.D., Christison Prof. of Therapeutics and Clinical Medicine, Univ. of Edinburgh. 3d ed. Pp. 324. Balt.: Williams & Wilkins, 1949. Price, \$5.00.

*Geriatric Medicine.* Edited by EDWARD J. STEIGLITZ, M.D., Attending Internist, Suburban Hospital, Bethesda, Md. 2d ed. Pp. 773; 180 figs. Phila.: W. B. Saunders, 1949. Price, \$12.00.

THE greatly increased interest in geriatrics in the 6 years since the appearance of the 1st edition naturally called for extensive revision and addition of new material. The 47 contributors have successfully maintained this work in its leading position.

# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

NOVEMBER, 1949

## ORIGINAL ARTICLES

### BLOOD TEMPERATURE AND ITS CONTROL\*

By H. C. BAZETT, M.D.  
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(From the Department of Physiology, Medical School, University of Pennsylvania)

BLOOD temperature is a term often used loosely, in which blood temperature is confused with body temperature. Blood temperature is usually thought to be regulated at some constant level. It is in no way constant. It shows great fluctuations from time to time and from place to place, and controlled fluctuations in peripheral vessels are utilized to regulate the temperature in the central vessels at a more or less constant level. The blood acts as a common carrier of heat from one area to another, a function which is incompatible with a constant thermal load. The regulation of this circulatory function appears to depend on at least 3 mechanisms: the direct reaction of blood vessels to temperature levels; reflex responses to thermal sensations; and the reactions of two reciprocal centers in the hypothalamus to the temperature levels to which they are exposed, through which the temperature of the blood supplying them is regulated. Malfunction of the whole mechanism is commonly attributed to simple failure of these higher centers; such a limited point of view is apt to

be inaccurate, and should not be adopted even tentatively.

The inconstancy of blood temperature, and its function as a regulating, rather than a regulated, factor, has been known since the days of Claude Bernard, who himself described it. However, the magnitude of these variations generally has not been recognized. Modern catheterization, with the use of non-wetting plastics, allows thermocouples to be left in place for hours, so that much more definite information has become available. Figure 1 illustrates such a thermocouple encased in a plastic tube of less than 0.5 mm. diameter and inserted 4.5 cm. up the brachial artery. It is quite easy to insert such catheters for 20 cm. or more and to reach the abdominal aorta or vena cava from the femoral region, or to travel along other similar vessels.

The variability of the *venous temperature* has been generally accepted, as has that of capillary blood. It is inconceivable that large temperature differences could exist between the blood in such vessels and the tissues, separated as they are by such thin membranes.

\* The fourteenth Hughlings Jackson lecture delivered at the Montreal Neurological Institute, McGill University, Montreal, on May 13, 1949, reviewing recent work supported by a Life Insurance Medical Research Fund Grant.

On the other hand, *arterial temperature*, with blood flowing rapidly to the periphery, is usually supposed to be relatively constant. Actual measurements<sup>8</sup> show such a conclusion to be quite erroneous except in a very warm environment. Thus temperatures have been observed as low as  $21.5^{\circ}\text{C}$  in the radial artery in a room at  $9^{\circ}$  to  $10.5^{\circ}\text{C}$ ,  $25.1^{\circ}$  in the dorsalis pedis in a room at  $20^{\circ}$ , and  $31.1^{\circ}$  in the brachial artery in a room at  $13.3^{\circ}$ . In the last case the low temperature was due in part to immersion of the limb

warmed. The close association of veins with peripheral arteries explains these anomalies, since the heat lost by the arteries should reheat the cooled blood in the veins. The falling gradients of temperature in the arteries are matched by rising gradients in the returning venous blood. Light compression of these veins below a point of measurement of arterial temperature interferes with their cooling effect on the artery above it and can cause a marked rise of arterial temperature. The exchange of heat between artery and vein has

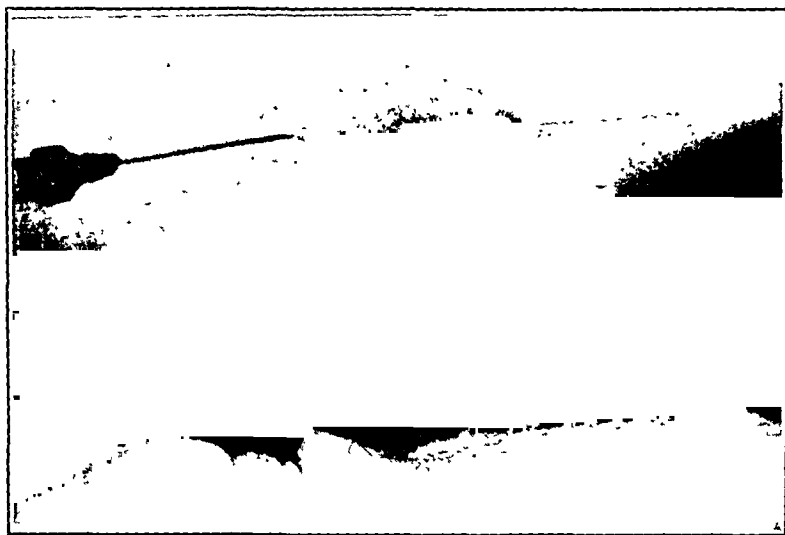


FIG. 1. Roentgenogram of plastic covered thermocouple introduced into the brachial artery.

distal to the point of measurement for short periods in cold water. That the environmental temperature affects the thermal gradients between the brachial and radial arteries, as well as their levels, is shown in Figure 2. This figure also indicates that arterial temperatures may be modified very readily by exposure of the limb to local cooling (or warming) considerably distal to the point of measurement.

Cooling of blood flowing in an artery of the degree indicated implies a large exchange of heat, yet surfaces of overlying arteries are not detectably

also been demonstrated in animal experiments by Dr. Leon Eisenberg<sup>12</sup> by the perfusion of cool saline into a vein. No extensive proof of this heat exchange is needed, since the known anatomical relationships of peripheral arteries with *venae comites* renders the existence of such exchange inevitable. Indeed this exchange appears to be the main function of the arrangement. It is surprising that its importance was not recognized earlier on mere theoretical grounds.

Other evidence of the large heat exchange exists. In a cool environment

the thermal gradient across the thin arterial wall is of the order of 1 to 2° C, which in itself indicates a large heat flow, since the insulation must be low. Also under conditions of rapid cooling particularly in readjustments to new conditions, large pulsatile changes in temperature within the arteries often may be seen, indicating that the system is reacting as a natural "thermostromuhr". Pressure pulsations cause pulsatile changes in blood flow and these in turn pulse-like changes in arterial temperature.

Examples of such pulsatile changes are shown in Figure 3. In the topmost record there was only a small thermal gradient between the brachial and radial (see graph for room conditions at 22° C of Figure 2), though a steeper gradient appeared to exist more distally

along the radial artery. Only slight "pulsations" in temperature are visible in the radial, while in the brachial only those accompanying extra systoles were readily detected. Three hours later the middle record was obtained when the arm had been recovering for 5 minutes after a 10 minute immersion of the hand alone (below both couples) in water at 2° C. At the signal on this record the hand and lower forearm were immersed in water at 2° C. The earlier cooling and rewarming had exaggerated the thermal gradients along the vessel and had increased pulsations. The second cooling temporarily decreased the pulsatile changes in the radial and caused a rise in brachial temperature, as vasoconstriction reduced the venous return. At the end of 5 minutes just before the signal in

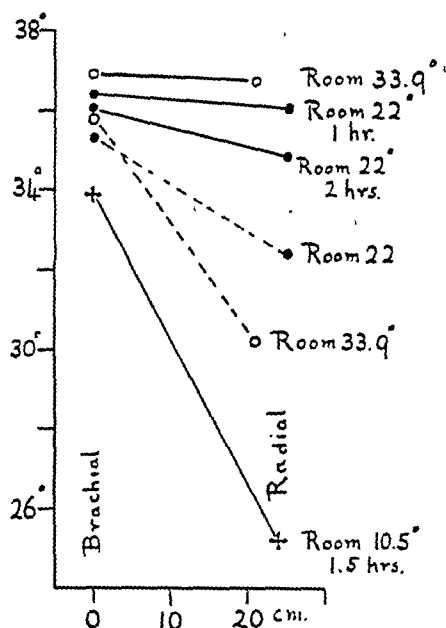


FIG. 2. Thermal gradients observed in a single subject between the brachial and radial arteries at different room temperatures (as indicated.) Values obtained in room temperatures of 33.9° and 22° C, which are connected with dotted lines, were obtained when the distal part of the limb had been cooled by immersion in cold water. In the former case this immersion was as stated previously and published<sup>8</sup> (Exp. 11 of that series), while that at 22° was as stated for records reproduced in Fig. 3. In both cases all or most of the cooling was applied distal to the thermocouples.

In the experiment in the room at 22° C, another couple had been inserted in the radial artery on the back of the hand close to the origin of the artery to the thumb. The temperature gradient in the 4 to 6 cm. length between the two couples in the radial appeared to be of the order of 4°.

the lowermost record, both radial and brachial temperatures had fallen, and the pulsations in the radial had regained their size, as the greater cooling of venous blood compensated for the slower rate of flow. The gradient shown in Figure 2 as occurring after cooling in a room at  $22^{\circ}$  is that recorded here. After the signal when the hand and forearm were immersed in water at  $18^{\circ}$  C, the increase in temperature produced a sensation of warmth with vaso-

dilatation (in spite of its low level) and the temporary rapid flow of very cold venous blood associated with a rapidly inflowing arterial stream gave greatly exaggerated pulsations.

Gravity can induce similar effects, as is illustrated by Fig. 4. An individual, who was somewhat cool and was lying in a semi-inclined position, held his arm horizontal at shoulder level, and then lowered it to his side at the time indicated by the signal. There

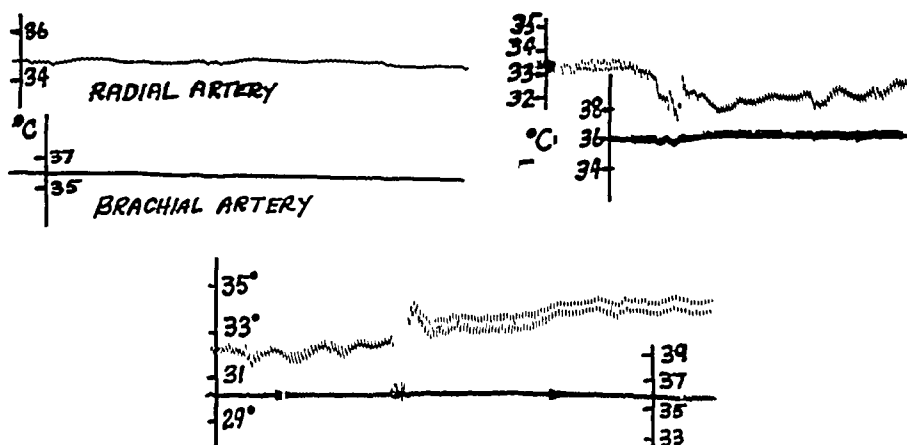


FIG. 3. Records of radial and brachial arterial temperatures measured in a room at  $22^{\circ}$  C ( $72^{\circ}$  F.) after exposure for 3 hours. The left upper record represents conditions after some earlier moderate cooling of the hand (distal to the couples) in water. The right upper record was obtained after the hand had been immersed for 10 minutes in water at  $2^{\circ}$  C and had been allowed to rewarm in air for 5 minutes. At the signal the hand, and on this occasion also the forearm, were immersed in water at  $2^{\circ}$  for 5 minutes. The whole section reproduced before and after immersion represents 100 secs., which indicates the time scale for all these records. The lowest record shows the end of this 5 minute immersion, which was followed at the time of the signal by transfer to water at  $18^{\circ}$  C.

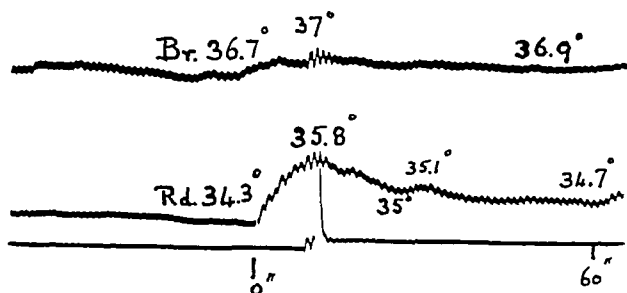


FIG. 4. The effect of lowering the arm from shoulder level to the side in a subject lying in a semi-inclined position, nude, in a warm room at  $28.3^{\circ}$  C ( $83^{\circ}$  F), after he had been cooled in a stirred water bath at  $33.2^{\circ}$  C ( $90^{\circ}$  F) previously for 35 minutes. The arm investigated was held supported throughout in air outside the bath.

resulted increases in temperature in both brachial and radial arteries, while the pulsatile changes in temperature originally visible in the brachial artery were reduced and those of the radial increased. Gravity effects presumably temporarily slowed venous flow in the veins adjacent to the brachial, so that heat exchange in this area was reduced. On the other hand, the resulting engorgement of the more peripheral veins exaggerated cooling of the blood in the radial. The exchange of heat between the arteries and veins was shifted to a more peripheral position. Yet the considerable thermal changes were not accompanied by any conscious sensation of temperature.

The changes described depend on circulatory adjustments through which cool blood returning in *venae comites* causes *precooling of entering arterial blood*. This allows an internal exchange of heat with supply of oxygen to the peripheral tissues and economy of heat loss. Attainment of a steady state seems compatible with considerable thermal gradients along the arteries, as well as along the axes of the limbs. On the other hand under such conditions gradients between the vessels and tissues are probably relatively small. Thus in warm rooms averaging some 26° C (79° F) Pennes<sup>21</sup> found brachial temperatures averaging 0.96° C below those of the rectum, while the deep tissues of the forearm had temperatures only 0.16° below that of the brachial. The longitudinal gradient in aggregate was considerable, the transverse relatively slight.

A mechanism through which precooling of arterial blood is brought about should be a considerable disadvantage in a warm environment. In such an environment it appears actually to be absent, for the temperatures observed on the surfaces of the tips of the fingers or toes may exceed those observed on more central surfaces<sup>16</sup>.

The return of venous blood through superficial veins, far removed from the arteries, which is so well recognized, would explain this adjustment, though this might be more effective if dilatation of superficial veins was associated with reciprocal constriction of the deeper channels. Reports have been made of experimental evidence of such reciprocal vascular reactions, possibly involving veins, present as a peripheral mechanism, even in the absence of all true reflexes. Such a type of control is surprising.

*Direct Reactions of Vessels.* J. R. Pappenheimer *et al.*<sup>20</sup> have described constriction of superficial cutaneous vessels and a reciprocal dilation of deep vessels when excised limbs are perfused with cooled blood. The condition is reversed when the blood is warmed. Also Perkins *et al.*<sup>22</sup> have demonstrated vasoconstrictor responses in the skin of dogs in areas which have been sympathectomized or denervated, if the skin surface falls below 22° C. In these cases the vasoconstriction appears to be due to direct effects on the vessels, rather than on axone reflexes. In all probability similar responses can develop in normal innervated skin in man, even though they are not always obvious. Thus exposure of hands to extreme cold has been repeatedly described as giving rise to severe pain, starting at a critical level of skin temperature of about 10° C, as in experiments testing gloves during the war period. The same temperature is regarded as a critical one by Aschoff<sup>1</sup> in experiments with hand baths, as vasodilator reactions commonly develop at temperatures below this level. This is also considered by Ungley<sup>27</sup> as a critical level for the development of immersion foot. In our experiments<sup>9</sup> pain has developed at or about these levels and this pain has often been preceded by an abrupt fall of temperature, suggesting vascular spasm. Dilator reactions often

have followed the pain, and have appeared to be inflammatory in character and of the axone reflex type described by Lewis<sup>15</sup>. In such reactions the temperature of a surface exposed to cold may be increased through 10° to 15° C in as many minutes. It seems improbable that this could happen, unless the venous return is directed up superficial veins (and away from the *venae comites*) also under such conditions.

*Reflex responses to thermal sensations* provide the mechanisms through which rapid reactions to sudden changes are attained. The existence of reflex vasoconstriction to cold is fully established. The reaction is relatively simple in that superficial vasoconstriction allows surface temperatures to fall, and thermal conductance is reduced. In consequence central temperatures in the trunk, and in the large arteries leaving the trunk, rise, as cooling by returning venous blood is reduced. Cooling effects are observed rapidly, and extend to peripheral areas not exposed to the cooling even if the blood supply of the cooled area has been occluded<sup>23</sup>.

Reflex responses to warmth are less definite and their existence has been denied<sup>23</sup>. Effects on distant areas are delayed for minutes. Occlusion of the vessels of the warmed area is usually claimed<sup>23</sup>, but not always<sup>10</sup>, to prevent any such general effects. The existence of reflex responses to warmth on the other hand has been claimed on the basis of vasodilatation accompanying a fall of rectal temperature<sup>17</sup>. Such evidence is not reliable, for, as will be seen later, rectal temperature is a poor index of hypothalamic changes. The discordant statements depend on failure to allow for the complexities imposed by vasodilatation. During such reactions in rewarming thermal conductance is increased and heat is distributed more evenly through the body,

so that some areas are warmed at the expense of others. Rises in temperature are strictly local, and usually are seen first in the cooler more peripheral areas<sup>24</sup>. Not only is the outflow of warm arterial blood accelerated but also the return flow of cooled venous blood. Consequently, the temperature of the blood in any given artery may at first either rise or fall, or vasodilatation may be evidenced by increased pulsatile changes in temperature without any alteration in the mean level. The utilization of a background of cooled skin, on which the effects may be demonstrated, may have contributed to the apparent long delays, since reflex vasodilatation probably cannot readily overcome a spasm due to direct cooling of the vessel.

The apparent prevention of general effects by the mere occlusion of the vessels of the warmed area is not surprising, for warming is an active process, not a passive one as is cooling. If the inflow of heat is prevented, any vasodilatation is apt to be evanescent. The increased thermal conductance speeds heat loss and the reaction therefore may be self-limiting.

The existence of reflex vasodilatation to warmth can be readily demonstrated by vascular temperatures, for an increase in arterial temperature in a properly chosen vessel may be demonstrated in a distant area with a latency of only 10 seconds, which entirely excludes any direct effect of temperature changes on the centers (unpublished data). The complexities are well demonstrated by the facts that rewarming of a hand after previous pronounced cooling can cause dilatation which shows itself by a sudden precipitous fall in brachial arterial temperature<sup>8</sup>. Similarly a rewarming of a cooled hand may cause a precipitous fall in temperature on the palmar surface<sup>9</sup>. Thus both increases and decreases in surface temperature may

indicate increased thermal conductance produced by vasodilatation, and the areas most favorable for demonstrating the increases are not always easy to predict.

*Thermal sensations* which give rise to vasoconstrictor or vasodilator reflexes are not dependent on the temperature levels in the skin. The well known phenomena of adaptation exclude such an hypothesis. Nor can they be explained as due to the rate and direction of change. If an arm be immersed in water warm enough to maintain the surface at a temperature significantly above that of arterial blood entering the arm, sensations of warmth continue indefinitely, even though a steady state is maintained. On the other hand lowering the temperature of such a bath for instance from 40° to 39° may give a temporary absence of warmth<sup>13</sup>. However, this sensation returns after the tissues just below the skin have had time to cool, and then again continues indefinitely. Thus the evidence indicates that the sensation arises as the result of the thermal gradients which are set up, and disappears as these are temporarily extinguished.

In order to obtain experimental reversal of these gradients Dr. McGlone and I many years ago investigated the thermal sensations generated in a double fold of prepuce where a recognizable thermal receptor could be stimulated from either side of the fold<sup>4,5</sup>. Normal sensations were generated from both sides, though the intensities of the sensations and their latencies varied. A simple gradient is inadequate to explain the phenomena, and it seems probable that the special arrangement of the vessels in the dermis described by Spalteholz<sup>25</sup> is concerned, as indeed he surmised<sup>26</sup>. Theories built on this basis have been discussed earlier<sup>7</sup>. Here it is only necessary to state that thermal

gradients observed in relatively thick skin demonstrate that this anatomical arrangement does affect heat distribution. It would appear that cold sensations are caused by alterations in the gradients superficial to the arteriolar plexus, and warm sensations by those just deep to it, where the deeper tissues are normally cooler than those more superficial. On such hypotheses the marked changes in arterial temperature that can occur in the larger and more central vessels should have little effect on the sensory mechanisms. This appears to be the case.

There remains a possibility that deep receptors of temperature exist, even though there is no obvious conscious sensation. If so, it is unlikely that receptors are situated in or near the vessels, for large exchanges of heat, such as those indicated in Figure 4, give no indication of having induced either sensations or reactions. In the prepuce sensory receptors for warmth can be identified as existing in the subcutaneous as well as in dermal layers. Deeper receptors might also occur in the subcutaneous tissues beneath the thicker skin of other parts of the body where probably they would not be recognizable as sensitive spots. While cold is purely an exteroceptive sensation, warmth can be either exteroceptive or proprioceptive, since heat may be generated in muscles. Deeper receptors might be concerned with heat of such internal origin. Even here gradients in temperature would probably act as the stimulus, since warming of deeper tissues by focused micro-wave radiation does not induce sensations of warmth<sup>14</sup>.

Sensations of temperature may be modified by various factors. Thus dilatation of the dermal vessels, however produced, not only modifies the thermal gradients in the skin, but also lowers the sensitivity to cold in spite of the raised surface temperature. Thus both



the threshold for stimulation and the latency of sensation are increased<sup>3,4</sup>. These observations have been confirmed and established firmly by Ebaugh and Thauer<sup>11</sup>, who, however, were unable to confirm any facilitation of sensations of warmth ascribed to vasodilatation on more slender evidence<sup>3</sup>. On the other hand vasodilatation does not appear to increase the latency for warmth as it does for cold<sup>4</sup>. Vasodilatation may cause increased heat capacity, and more rapid thermal conduction; conditions are complex. Sensations are also modified by carbon dioxide in a way which may be dependent on the vascular reactions. Thus water baths charged with carbon dioxide do not feel as cold as do normal baths at the same temperature. Inspiration of carbon dioxide may also cause a wave of sensation of warmth, which is attributed in consciousness to dermal tissues. Heat directly conducted to the subcutaneous tissues from the muscles either by veins or arteries may be responsible for sensations of warmth which accompany exercise. These are usually associated with the occurrence of sweating in the limbs during work, even if the individual is exposed to an extremely cold environment.

No emphasis need be placed here on the well recognized characteristics of spatial summation and adaptation that are found in thermal sensations. It should be noted, however, that adaptation in this case does not appear to be a property of the receptors, so much as one of the accessory mechanisms of the stimulus. Thermal sensations fade when the thermal gradients are reduced, as the thermal changes spread more deeply. They persist indefinitely, if the circulation of blood at normal temperature to a locally heated area maintains an adequate gradient. Adaptation is more pronounced with cold stimuli, since the slowed blood flow which accompanies vasoconstriction, is unable

to maintain the thermal gradients. Thermal stimuli may, therefore, be compared with those of light. This causes adaptation in the eye by bleaching rhodopsin, thus also affecting an accessory rather than a receptor mechanism. It would, however, be rash to generalize and apply such conclusions to other receptors, for each receptor appears to be adjusted to its own function and many different mechanisms may be utilized.

Sensory receptors for temperature appear to be stimulated also by other forms of stimulus, for release of vascular stasis may generate intense sensations unassociated with measurable thermal changes<sup>6</sup>. Possibly osmotic or chemical stimuli are involved.

*Regulation of hypothalamic temperature by the blood stream* appears to be attained by the adjustment of the temperature of the inflowing blood supplying these tissues. Several measurements of the temperature within the right internal jugular bulb have been made in man, and this temperature has usually been found some 0.2° above that simultaneously observed in external iliac arteries. In view of the high metabolism of the brain this is not surprising. In one experiment a thermocouple was left in place for hours in this vessel, so that its temperature could be compared with those observed in the rectum, external iliac, femoral and dorsalis pedis arteries, and with that at the distal end of the inferior vena cava. The individual was inadequately clothed below the waist, and was lying in a room at 20° C (68° F), so that cooling occurred, while the heat loss was mainly from the lower limbs. After several hours of such cooling the subject was rewarmed by immersion of both hands and forearms in hot water, so that rewarming depended on heat acceptance by the upper limbs.

Comparison of the internal jugular temperature with that of the rectum

after about one hour's exposure showed identical temperatures, probably due to a more rapid cooling of the jugular bulb. Later the rectal temperature always remained the lower, when the delay in its cooling had been overcome. The hypothalamic temperature variations were of the same order of magnitude as those of the rectum but occurred much more abruptly, since they were less damped by large heat capacity effects. Owing to these differences in the time characteristics, differences as great as  $1.4^{\circ}\text{C}$  ( $2.5^{\circ}\text{F}$ ) were set up (in favor of the jugular bulb over the rectum) during warming, and reduced to  $0.6^{\circ}\text{C}$  ( $1.1^{\circ}\text{F}$ ) on recooling. The latter difference increased again to over  $1^{\circ}\text{C}$  as the cooling effects approached more nearly to a steady state. The temperature of the jugular bulb, which probably reflects that of the hypothalamus, is therefore by no means steady but swings more readily and more rapidly than does that of the rectum. It may not be entirely protected from local influences since drinking two cups of hot tea raised the temperature of the jugular bulb by  $0.5^{\circ}\text{C}$  in 5 minutes, while the temperature in the external iliac artery, inferior vena cava and rectum were much less affected. While the hypothalamic temperature may be regulated, it is by no means free of fluctuations.

The regulation of fluctuations in temperature in peripheral vessels are such as to induce smaller changes in the temperatures of central vessels, such as would tend to return the hypothalamic temperature to its normal level. These temperatures in the larger arteries are similar to those found in the jugular bulb, though their levels are somewhat lower. Like the fluctuations of the jugular bulb, they occur more readily and more abruptly than do fluctuations in the rectum. The temperatures existing in these central arteries induce relatively constant and similar

levels of temperature in the central areas of the body, namely the thorax, abdomen and cranium. Thus central body temperature is controlled. However, these central temperature levels are not precisely identical under conditions of asymmetrical cooling, such as that used in this experiment. Here the temperature in the external iliac artery and inferior vena cava commonly were  $0.1^{\circ}$  to  $1.1^{\circ}$  above that of the rectum, while the temperature of the femoral artery just below Poupart's ligament might be  $0.8^{\circ}$  above or below that of the rectum. Considerable effects of local warming and cooling were in evidence in both the external iliac and femoral arteries, and to a small degree in the inferior vena cava.

One could probably accept temperatures in the abdominal aorta at the level of its bifurcation as representing approximately central arterial temperature. This is a point readily reached with thermocouples. Distal to this, steep thermal gradients may develop. Thus at the end of this experiment a gradient of  $1^{\circ}\text{C}$  was to be found in the iliac vein in a distance of 4 cm. (between points 6.5 cm. and some 2.5 cm. above Poupart's ligament). Deep rectal temperature is probably closely related to temperatures observable in the iliac arteries and veins just central to Poupart's ligament; it does not represent a true central temperature unaffected by local changes.

**Summary.** One may conclude that current theories of thermal control are not grossly in error, even though the evidence on which they are founded, is by no means reliable. A theory, such as that advanced years ago by Meyer<sup>18</sup>, supposing the existence of two opposing centers, one in the anterior hypothalamus controlling heat dissipation and one lying more posteriorly controlling heat conservation, still seems adequate. Presumably the former center is stimulated by sensations of

warmth and has an optimal temperature for activity, which lies above the normal hypothalamic temperature, while the latter is stimulated by sensations of cold and has an optimal temperature below the normal level. The combination of reactions initiated either reflexly or centrally through these centers is reinforced and maintained also by local reactions of the cutaneous and deeper blood vessels themselves to temperature levels, as far as the vascular components of the reaction are concerned.

Such an hypothesis, however, fails to account for regulation of central body temperature at higher levels during exercise, as described by Nielsen<sup>19</sup>. Such levels vary with the metabolic

loads imposed by the work and appear to induce higher temperatures for the working muscles at the higher loads. These changes seem to be beneficial and to aid efficiency<sup>2</sup>. This adjustment, if properly understood, might throw light on the underlying mechanisms of thermal control in general. It might equally be induced by modifications of peripheral sensation as by alterations in the hypothalamic centers. However, the effects of carbon dioxide on skin sensations and of exercise on sweating seem to oppose any theory of a peripheral origin for the phenomenon. The mechanisms concerned in such adjustments remain completely unknown.

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# EXOPHTHALMIC GOITER IN CHILDREN: TREATMENT WITH PROPYLTHIOURACIL

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THE cause of exophthalmic goiter remains a mystery despite the great advances that have been made in its diagnosis and treatment. We are fortunate that treatment, even though essentially empirical, is usually successful.

Exophthalmic goiter in children presents all the problems of exophthalmic goiter in the adult, plus others due to immaturity, active growth, and changing metabolism. In this paper we wish to discuss our experiences with 26 cases of hyperthyroidism in children 16 years of age or younger. Eight of these have been treated with thiouracil or propylthiouracil. These we will consider in detail to show some of the responses to this type of therapy.

Diagnosis of hyperthyroidism in children is based on symptoms, signs, and basal metabolic determinations.

Symptoms are of two types: 1, those that are similar to those of adults and, 2, those that may be present or are more prominent in young people. The majority of children have signs and symptoms identical with those of adults, including symmetrical enlargement of the thyroid gland with thrill and bruit, exophthalmos, tremor, either actual weight loss in spite of ravenous appetite or weight remaining stationary when it should be increasing, nervousness, tachycardia, palpitation, warm and moist skin, general weakness, easy fatigability, quadriceps weakness, heat intolerance, elevated systolic and low

or normal diastolic blood pressure, dyspnea, dorsal curvature of the distal phalanges, and irritability.

Certain other complaints may be prominent in children and may be quite misleading in the making of an accurate diagnosis. Important in this group are gastrointestinal symptoms (nausea, vomiting, and different types of abdominal pain), high susceptibility to upper respiratory infection, delayed or irregular menses, sleep disturbance (insomnia, restlessness, or talking in sleep), frequent epistaxis, marked personality changes with nervousness, temper tantrums, crying spells, headaches, and fainting. These children often give a history of an enlarged thyroid gland for from one to several years and may have been taking iodine for colloid goiter. The blood pressure findings are significant in children, 140 over 50 being a typical recording. The frequency of upper respiratory infections in some of these children increases the difficulty of getting a basal metabolic determination that is accurate.

Treatment must be suited to the individual case. There are 3 types of therapy: rest, operation and drugs, which may be used singly or together, depending on the individual need.

A program of rest with discontinuance of school, restricted activity, long hours of sleep with frequent daytime rest periods, a high caloric diet, and, if necessary, mild sedation is valuable. This frequently will alleviate the symp-

toms and carry a young patient along until he is a little older before undergoing operation. An occasional patient with mild toxic symptoms of short duration may be treated solely by this method. Adequate attention to psychosomatic aspects of the disease and to the education of the parents is essential in such a program.

As in adults, the surgical treatment of exophthalmic goiter in children gives excellent results in a high percentage of cases. Indications for operation are (1) the determination, based largely on experience, that operation is the best treatment for the particular patient; (2) failure of medical therapy, including a lack of response and development of complications such as leukopenia; and (3) persistence of an enlarged gland in spite of regression of toxicity after medical therapy.

Careful preoperative preparation is essential to successful surgery, including a rest program as outlined above, combined with the use of iodine and antithyroid drugs, such as propylthiouracil and methylthiouracil. Propylthiouracil causes a marked increase in the vascularity of the gland, making operation technically difficult. When antithyroid drugs are used, they should be discontinued 2 weeks prior to operation and iodine should be used to involute the gland. Iodine alone is excellent in the preoperative preparation of these patients, and for the past year we have used Lugol's solution only, without propylthiouracil, except in the most toxic cases. Operation should not be performed until the patient is gaining weight, the pulse rate has decreased, the basal metabolic rate is declining, and toxic symptoms are in remission.

Subtotal thyroidectomy is the operation of choice. In this clinic we have used superficial cervical nerve block anesthesia since 1928, in preference to the older method of infiltration. We use

1½% procaine with no adrenalin. Children 12 years of age and older given adequate preoperative sedation (pan-topon, scopalamine, and nembutal, the dosage depending on weight and age) tolerate this well. The same surgical technique is used as in adults, this being an intracapsular excision of hyperplastic thyroid tissue, preferably with the electro-surgical knife. Considerable time and effort is spent prior to operation obtaining the confidence of the child, and the fact that no general anesthetic has ever been used testifies to the success of these efforts.

Postoperative care is extremely important. One advantage of nerve block anesthesia is that the patient is able to cooperate immediately and be given frequent oral doses of Lugol's solution. Ten to 15 doses of 10 drops of Lugol's solution are given on the day of operation, 4 doses in the first postoperative hour, 10 doses the second day, and 3 times a day thereafter until discharge. Rarely it may be necessary to give iodine subcutaneously, by proclysis or by duodenal tube. We do not use it intravenously. Iodine therapy after discharge from the hospital depends on the response of the patient. In some cases it may be discontinued after weeks, and in others it may have to be used for months or occasionally indefinitely.

The program of rest and high caloric intake is essential with the gradual increase in activity. We have found that the patient's weight is the best index of response to treatment and insist that a substantial gain be made the first 3 months after operation.

Medical treatment of hyperthyroidism is much in vogue, with thiouracil, thiourea, thiobarbital, propylthiouracil, and methylthiouracil receiving the most attention. Radioactive iodine is receiving much study, but results have been variable, some patients showing early favorable response only to relapse later.

In others the response has been encouraging but sufficient time has not yet elapsed to consider the patient cured.

We have used thiouracil and propylthiouracil on 8 of these patients. Response has been so varied that a brief individual discussion of each case is necessary. For the past 2 years propylthiouracil has entirely replaced thiouracil in our therapy. These will be discussed in the chronological order in which we saw the patients in order to show the changes in concepts.

her toxic symptoms increased. On October 10 her basal metabolic rate was  $+33\%$ . She was placed on thiouracil, 0.1 gm. twice a day. She stayed on this dosage until June 8, 1945, when the drug was stopped. At this time she had gained 15 pounds, was free of toxic symptoms, and had a basal metabolic rate of  $+7\%$ . She got along satisfactorily until Feb. 28, 1946, when symptoms recurred. She lost  $7\frac{1}{2}$  pounds, and her basal metabolic rate was  $+24\%$ . She was put on thiouracil, 0.1 gm. twice a day. On April 11 her white cell count was 4,150 and thiouracil was stopped. On May 2 it was found that she had lost 2½ pounds and her blood pressure was 142 over 62, and her pulse was 132. On July 22



CASE 1. (a) Exophthalmic goiter in 12 year old girl who has a basal metabolic rate of  $+33\%$  and is 21 pounds underweight. (b) Same patient 2 months after antithyroid therapy. Her basal metabolic rate is  $+5\%$  1 year after stopping therapy.

**Case Reports.** CASE 1. H. B., a white female aged 12 years, was first seen on Sept. 9, 1944. She had an exophthalmos of 3 months' duration and swelling of the neck for 2 months, along with palpitation, extreme nervousness, and tachycardia, and was 21 pounds underweight. She had been taking iodostarine for 2 months. Her basal metabolic rate was  $+10\%$ . It was thought clinically that she was probably iodine-fast. She was observed for a month, during which time

she was placed on propylthiouracil, 25 mg. 3 times a day. Five weeks later her white blood count was 4,060. In December, 1946, propylthiouracil was discontinued as she was well. She has remained well since.

CASE 2. R. N., a 12 year old white female, was first seen Sept. 4, 1944, having been ill 2 years. She was 23 pounds underweight and had a ravenous appetite, alternating diarrhea and constipation, tremors, nervousness, "heart pains", and temper tantrums. Her

blood pressure was 118 over 55 and her pulse 110. She was hospitalized and placed on thiouracil, 0.1 gm. 3 times a day. On November 1, she developed a skin rash on her thighs. Thiouracil was discontinued. She was placed on Lugol's solution and prepared for operation, and on December 18 a right lobectomy and isthmectomy were performed. On March 3 the left lobectomy was done. She made excellent recovery. On August 27 a nodule was felt in the right upper lobe. On June 26, 1947, her neck was enlarged and toxic symptoms recurred. She was placed on propylthiouracil, 50 mg. 3 times a day. On July 12 her white blood cell count was 4,200, but she was continued on the drug. Her disease was controlled with propylthiouracil until May, 1948. On June 2, 1948, operation was performed again for a large hyperplastic

pounds. She was placed on propylthiouracil, 25 mg. three times a day. In September she went back to school half time. In April, 1947, she was without propylthiouracil for three weeks, lost 4½ pounds and became hyperactive. Propylthiouracil was resumed until June 29, 1947, when it was discontinued. At the present time, 16 months later, she is well and is attending school all day and weighs 114 pounds, has a pulse of 90, and a blood pressure of 125 over 60. Her metabolic rate was +10%. This is the most satisfactory result of propylthiouracil therapy we have seen in either an adult or a child and shows, despite statements in the literature to the contrary, it is at least possible to arrest the disease in some instances. One always hesitates to speak of a cure in exophthalmic goiter by any manner of treatment.



CASE 2. (a) Severe case of exophthalmic goiter in 12 year old child. Following skin eruption from thiouracil, a thyroidectomy was performed. (b) Same child developed a recurrence 3 years later that failed to respond to propylthiouracil. After further surgery the disease is arrested, and the basal metabolic rate remains normal.

gland. Seven days later she was discharged with a basal metabolic rate of +10% and a pulse of 72.

CASE 3: A. F., a 10 year old white female, was first seen Feb. 2, 1946. She had an enlarged thyroid gland, an exophthalmos of 2 months' duration, tremor, warm moist skin, and a ravenous appetite. Three weeks before her metabolic rate was reported as +62% at another institution. After three weeks of iodine it was +24%. Her blood pressure was 140 over 60, her pulse 120, and her weight 85

CASE 4. M. T., a white female aged 8 years, was first seen Sept. 14, 1946. Symptoms were extreme nervousness, insomnia and restless sleep, tremendous appetite, intolerance to heat, frequent sore throats, enlarged thyroid gland, tachycardia, and quadriceps weakness. Her blood pressure was 126 over 50 and her pulse was 158. She was placed on Lugol's solution for 2 weeks. She gained 3½ pounds, was less nervous, and felt better. On September 25 she was started on propylthiouracil, 25 mg. twice a day. Slow improvement oc-

curred until Jan. 18, 1947, when she contracted infectious hepatitis, as did her parents and several classmates. Propylthiouracil was stopped and she was placed on iodine for one month; then propylthiouracil was resumed and improvement continued. In February, 1948, she was free of symptoms, but her thyroid gland seemed larger than ever. In July, 1948, she appeared clinically well, and her basal metabolic rate was normal, so the drug was discontinued. In 4 weeks her basal metabolic rate had risen to +33%, and she was losing weight and becoming toxic, so the drug was again resumed. She again became normal. Further observation is warranted, but operation will probably eventually be necessary.

25 mg. 4 times a day. By April 21 all symptoms of hyperthyroidism were gone and she had gained 19 pounds. However, her thyroid gland continued to be greatly enlarged. On May 5, 1947, a subtotal thyroidectomy was performed on a large hyperplastic gland containing some adenomatous tissue. Since then she has remained well but has been on a reducing diet as she gained too much weight. She was continued on iodine for 6 months. Her last basal metabolic rate on Jan. 6, 1949, was +29%.

CASE 6. R. S., an 11 year old white female, was first seen Nov. 2, 1946. Her neck had been enlarged for 8 months, she was extremely nervous, exophthalmos was present, and there



CASE 3. (a) Exophthalmic goiter in 10-year old child who is on the verge of crisis and whose basal metabolic rate is +62%; weight 85 pounds; and pulse, 140. (b) Same child after stopping all therapy; basal metabolic rate, +10%. She received propylthiouracil for 1 year. She now appears clinically well, weighs 128 pounds, and has a pulse of 74.

CASE 5. N. R., a 13 year old white female, was first seen on Sept. 30, 1946, with symptoms of nervousness, heat intolerance, palpitation, weight loss, and increased appetite. Before our examination she had been on iodine for 2 months and thiouracil for 2 weeks with no improvement. She had a greatly enlarged thyroid gland with no thrill or bruit. Her pulse was 120 and her blood pressure was 142 over 40. There was stare but no exophthalmos. She was quite toxic. She was hospitalized and placed on propylthiouracil,

was a 13 pound weight loss in 6 months. She had been on Lugol's solution for 7 months. Her basal metabolic rate was +35%; her blood pressure, 134 over 44; and her pulse, 128. She was placed on propylthiouracil, 50 mg. twice a day. Twenty-two days later her white blood count was 2,500. The drug was discontinued, and she was placed on Lugol's solution. At this point contact was lost with the patient.

CASE 7. P. U., a 16 year old white female, was first seen Feb. 20, 1947. She had been



well until Jan. 23, 1947. At that time she was hospitalized for 2 weeks with symptoms of nausea, vomiting, diarrhea, and fever. She had had tachycardia and weakness of the legs since then. She had a moderate tremor, a pulse of 148, a blood pressure of 144 over 24, a weight loss of 14 pounds in 2 weeks, a warm moist skin, symmetrical enlargement of the thyroid with thrill and bruit, and quadriceps loss. A systolic murmur was present over the aortic and mitral areas. She had been on thiouracil for 10 days before admission. This was changed to propylthiouracil, 50 mg. 3 times a day. Three months later on April 22 she had gained 10 pounds; her blood pressure was 128 over 70, and her basal metabolic rate was +11%, and all toxic symptoms were gone. On July 23 propylthiouracil was discontinued. On August 26 her symptoms had returned.

She was definitely hyperthyroid with a basal metabolic rate of +43%. She was placed on iodine, and on September 10 a subtotal thyroidectomy was performed. She made a normal recovery, and when seen on May 27, 1948, she was well. She was continued on iodine until September 13. On Nov. 13, 1948, she resumed Lugol's solution, at which time her basal metabolic rate was +35%. There was a weight gain of 22 pounds, and she appeared normal.

CASE 8. M. G., a 16 year old white female, was first seen on Dec. 12, 1947. For 5 months she had been under her doctor's care for nervousness and loss of "pep". She had been told she had a goiter and had been given iodine. She had gained 11 pounds during this time but felt no better. She was jittery and constantly making purposeless movements. She was intolerant to heat and fainted frequently. She had a pulse of 116, a blood pressure of 142 over 60, exophthalmos, moderate tremor, and a symmetrically enlarged thyroid with thrill and bruit. In addition, for 6 months she had had definite voice change; it had become husky and gave her poor enunciation. Her basal metabolic rate was +49%. On December 2 she was started on propylthiouracil, 50 mg. 3 times a day. On January 3 she was worse; there was a 6 pound loss of weight, a basal metabolic rate of +70%, and increased nervousness. Propylthiouracil had been stopped 2 weeks before because of a white blood cell count of 4,500. It was thought that she was on the verge of a thyroid crisis. She was hospitalized and placed on Lugol's solution. On Jan. 16, 1948, a subtotal thyroidectomy was performed on a large hyperplastic intrathoracic goiter. One month later her basal metabolic rate was 0%; pulse, 70; and blood pressure, 120 over 84. There was a weight gain of 18 pounds. Since then

she has been well, except that a reducing diet has been necessary.

In all of these cases the patient was placed on a regimen of rest, high caloric diet, and discontinuance of school, in addition to medication.

**Summary and Conclusions.** Twenty-six cases of exophthalmic goiter have been observed in children ranging in age from 8 to 16 years. Symptoms and treatment have been discussed, especially the results of thiouracil and propylthiouracil in 8 cases so treated. The following conclusions seem warranted:

1. Depression of white blood cells must be carefully watched for in the use of thiouracil and propylthiouracil. Four of 8 patients treated with these drugs developed white counts below 5,000, although there were no serious complications. Propylthiouracil is much safer than thiouracil, which should no longer be used.

2. These drugs have a goitrogenic action as evidenced by Cases 4 and 5, in which, although toxicity was relieved, the continuing large size of the gland made it necessary to perform thyroidectomy.

3. Early diagnosis in some cases may be difficult, for two reasons: 1, atypical symptomatology; and, 2, the masking of the clinical picture by previous treatment.

4. Individual response to these anti-thyroid drugs is uncertain in children, and there is no rule to determine in which cases they will be successful.

5. At present, the best place for these drugs is probably in preoperative preparation, or in patients in whom it may be necessary to delay operation.

6. The fact that in only one patient with hyperthyroidism was the disease apparently permanently arrested by propylthiouracil indicates that operation is still the method of choice in the treatment of these patients.

7. Iodine should be given to all patients prior to and following opera-

tion. Its use is especially indicated following propylthiouracil to decrease the vascularity of the gland and reduce bleeding at operation.

8. Cervical nerve block anesthesia was successfully used in all patients requiring thyroidectomy, no general

anesthesia being necessary. 9. These patients must have an even more careful postoperative regimen than that required for adults. The importance of a high caloric diet, restricted activity, rest, and iodine is stressed.

# LIVER AND KIDNEY FUNCTION IN ROCKY MOUNTAIN SPOTTED FEVER\*†

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ROCKY MOUNTAIN spotted fever is a severe generalized infection which is known to cause damage to many organs. Cases are now recognized with some frequency over wide areas of the United States. More instances of the disease are reported currently from the eastern seaboard and southeastern states than from the west. The *anatomic changes* produced can be demonstrated by pathologic techniques at autopsy. Disturbances of function have been observed clinically in the course of the disease, but few attempts have been made to evaluate the *physiologic alterations* in specific organs. We have previously described alterations in the serum proteins and in electrolytes of the blood, as well as the circulatory changes occurring in the disease<sup>10,13</sup>. These observations suggested that some functions of the liver and kidney might be disturbed.

In the treatment of infectious diseases, chemotherapy or specific immunotherapy is directed toward eradication of the etiologic agent. Such therapy is not aimed primarily at the prevention or control of physiologic disturbances which are induced in the host by the infectious process. In the hope of

obtaining information which would permit supportive therapy to prevent or correct such disturbances, studies of several functions of the liver and kidney were done to determine: 1, the degree of the physiologic disturbances; 2, their relation to the clinical severity of the disease; 3, the time in the course of the disease at which changes are maximal; and, 4, the degree to which function is restored with recovery.

PLAN. During the years 1942 to 1947 inclusive, 26 cases of Rocky Mountain spotted fever have been studied intensively in the North Carolina Baptist Hospital; 19 additional cases were seen for too short a period of time to be included in this report. Of the patients studied intensively, 16 were under the age of 15 years and were cared for on the pediatric service; the remaining 10 were treated on the medical service. Eight patients—5 children and 3 adults—were studied before the addition of high protein diets with vitamin supplements to our program of supportive therapy; 18 patients—11 children and 7 adults—were studied after this form of therapy was made routine<sup>11</sup>. Seven cases were classified as mild, 10 as moderately severe, and

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† Doctors William L. Venning and Weston M. Kelsey assisted in the care of the pediatric patients.

6 as severe; 3—all in children—were fatal. The criteria for classification of the cases have been previously published<sup>12</sup>.

The attempt was made to perform studies on each patient at 4 periods in the course of the disease: (1) as soon as possible after admission to the hospital, (2) at the clinical peak of the disease, (3) during convalescence in the hospital, and (4) during recovery after discharge. Since so many of the patients were small children and so many were critically ill—often comatose, edematous, and incontinent—it was difficult to do all of the studies planned on each patient. Furthermore, many patients were admitted when the disease was well advanced and were near the clinical peak when they were first seen. Only a few returned after recovery. Data on two or more periods are available in about one-third of the cases; 8 patients had serial liver function studies made at two periods, and 8 had kidney function tests at two periods.

**Methods. TESTS OF LIVER FUNCTION.** Studies were designed to measure carbohydrate conversion and storage by the oral galactose tolerance test; "detoxification" by the conjugation of orally or intravenously administered sodium benzoate to hippuric acid; the formation of proteins by the prothrombin time and the albumin and globulin levels; pigment metabolism by the quantitative serum van den Bergh test and the removal of intravenously injected bromsulfalein.

The *galactose tolerance* was judged to be abnormal if more than 3 gm. of reducing substance was excreted by the kidney in 5 hours following the ingestion of 40 gm. of galactose on a fasting stomach.

The excretion in 4 hours of at least 2.7 gm. of *hippuric acid*, calculated as sodium benzoate, after the oral administration of 5.9 gm. of sodium benzoate, was taken as normal. The excretion of 0.7 gm. in 1 hour after the intravenous injection of 1.77 gm. of sodium benzoate was likewise regarded as normal.

In children the adult doses were used for both the galactose tolerance and the hippuric acid tests; the normal range of values is less

firmly established in this age group, but for the purpose of this experiment the normal values were considered the same as in adults.

The *prothrombin time* was determined by the Quick method in adults and by a micro-method in children<sup>21</sup>. If the prothrombin time was prolonged, vitamin K was administered orally or parenterally and its effectiveness evaluated by serial determinations; 1 mg. of menadione per day was included in the high-protein supplementary feeding which was administered routinely to all patients after July, 1944. A prothrombin activity (control in seconds/prothrombin time) of less than 85% was regarded as abnormal<sup>22</sup>.

Serum levels of *albumin and globulin* were determined by the micro-Kjeldahl technique. Values below 3.5 gm. % for albumin or 1.5 gm. % for globulin were taken as abnormal.

For the *bromsulfalein (BSP) test* 5 mg. per kg. of body weight was injected intravenously; as many blood samples as possible were drawn after 5, 10, 15, 30, 45 and 60 minutes. Because of the difficulty in finding veins, especially in the children, only 2 or 3 samples were usually obtained. Retention of more than 10% of the dye at 15 minutes, 5% at 30 minutes, or any at all after 45 minutes was taken as evidence of abnormal function.

*Serum bilirubin* was measured by the standard van den Bergh technique; values above 0.8 mg. per 100 cc. were regarded as abnormal.

**TESTS OF KIDNEY FUNCTION.** The excretory power of the glomeruli was measured by urea clearance tests and nonprotein nitrogen (NPN) determinations; the excretory power of the tubules by phenolsulphonphthalein (PSP) tests; and damage permitting the escape of elements from the blood by the presence of albumin in the urine and by microscopic examination.

The *urea clearance* was determined by comparing the urea nitrogen in the blood with that in a sample of urine collected over a period of at least 6 and usually 12 hours; standard analytical techniques were employed. A value of 50% or less of normal was interpreted as indicating abnormal function; a value above 70% was accepted as indication of adequate function. Values between 50 and 70% of normal were interpreted as demonstrating questionable renal damage.

*Phenolsulphonphthalein (PSP)* excretion was determined in specimens of urine voided 15, 30, 60, 90, and 120 minutes after the intravenous injection of 1 cc. of dye. Excretion of 65% or more of the dye in two hours was regarded as normal in adults. The same dose was used in children, but an excretion

of 50% was judged to be normal.

Blood levels of *nonprotein nitrogen* were determined by standard methods. Values above 40 mg. per 100 cc. were regarded as abnormal.

Tests for *urinary albumin* were performed by boiling a sample of urine after the addition of acetic acid.

*Microscopic examination* of the urine was done on 15 cc. samples of voided urine; the samples were centrifuged in adults, but not in children.

**Results.** The results are summarized in the table. In order to save space, detailed data are not included; in the

simultaneous hippuric acid tests showed a decrease in function.

*Hippuric acid* excretion was satisfactorily determined in 16 cases. In 5 cases multiple tests were done. In 13 patients the hippuric acid excretion was less than normal at some time, usually at or just after the clinical peak of the disease, about the third week of rash. In 6 instances less than 1 gm. was excreted on the oral test. Nine tests gave normal values. In no instance was the hippuric acid excre-

TABLE 1. THE NUMBER AND SEVERITY OF CASES STUDIED COMPARED WITH THE NUMBER SHOWING ABNORMALITIES OF FUNCTION BY THE TEST INDICATED

|                             | Number of Cases Studied |          |       | Number with Liver Damage |     |         | Number with<br>Kidney Damage<br>Urea Clearance |
|-----------------------------|-------------------------|----------|-------|--------------------------|-----|---------|--|
|                             | Adults                  | Children | Total | Hippuric                 | BSP | Albumin |  |
| Fatal                       |                         | 3        | 3     | 1                        | 1   | 2       | 1  |
| Severe                      | 2                       | 4        | 6     | 1                        | 1   | 3       | 2  |
| Moderate                    | 4                       | 6        | 10    | 5                        | 2   | 9       | 4  |
| Mild                        | 4                       | 3        | 7     | 3                        | 2   | 4       | 2  |
| TOTAL                       | 10                      | 16       | 26    | 10                       | 6   | 18      | 9  |
| Before high<br>protein diet | 3                       | 5        | 8     | 6                        |     | 7       | 5  |
| After high<br>protein diet  | 7                       | 11       | 18    | 4                        | 6   | 11      | 4  |
| TOTAL                       | 10                      | 16       | 26    | 10                       | 6   | 18      | 9  |
| Before clinical peak        |                         |          |       | 0                        | 2   | 8       | 4  |
| At clinical peak            |                         |          |       | 6                        | 1   | 8       | 2  |
| After clinical peak         |                         |          |       | 4                        | 3   | 2       | 3  |
| TOTAL                       |                         |          |       | 10                       | 6   | 18      | 9  |

analysis of data in some instances where different tests were done on successive days, they have been considered as if they were done on the same day.\* Despite the unavoidable lack of baseline tests made before the illness began, a measure of control was afforded by the return to normal values after recovery and by comparison with figures for similar tests performed in other infectious diseases.

**TESTS OF LIVER FUNCTION.** *Galactose tolerance tests* were done on 9 patients and were repeated in 4 patients. All gave a negative reaction. In 5 instances

tion abnormal after the twenty-first day of rash. In 2 patients with abnormal tests the hippuric acid excretion reverted to normal before discharge. In general the defect in conjugation paralleled the clinical severity of the disease, though 3 patients with mild cases did have abnormal tests. In 3 instances simultaneous NPN determinations were above 40 mg. per 100 cc., while in 5 instances the NPN was normal. Simultaneous PSP tests gave normal values in 3 cases.

The *prothrombin time* was determined in 11 patients. In 5 cases the

\* Detailed data are available and figures on specific tests in an individual can be furnished on request.

prothrombin time, at some time during the course of the illness, was increased five seconds or more as compared with the control; the prolongation usually occurred at about the clinical peak of the disease. Only 2 patients had markedly abnormal tests, however. The percentage of activity in these 2 patients was 10 and 13%; in the remaining 3 cases the activity was 55 to 78%.

One child, who had a normal prothrombin time on admission, received prophylactic oral doses of menadione (1 mg. daily) for 5 days. At the end of that time (tenth day of rash) the prothrombin time was two minutes against a control of 14 seconds (18% activity), and the following day it was 3 minutes against a control of 18 seconds (10% activity). Within 12 hours after 1 mg. of vitamin K was given parenterally, the prothrombin time returned to normal and remained so. One boy had a slightly elevated prothrombin time on admission. One day later the prothrombin time was 2 minutes and 30 seconds, in comparison with a control of 20 seconds (13% activity). The prothrombin time remained at this level for 7 days (from the third to the tenth day of rash) in spite of the daily parenteral administration of 4 mg. of vitamin K. Both of these cases were classed as severe.

In all instances the prothrombin time was normal by the time of discharge from the hospital.

Serum levels of *albumin and globulin* were determined in all but 2 patients. In these 2 the total serum proteins were below 5 gm. %; they rose to 6.5 gm. by discharge. Albumin values below normal were found at some time in 18 out of 24 patients; in 7 they returned to normal by discharge. Reduced globulin levels were found in 4 patients; in 2 the value returned to normal by discharge. In 2 patients globulin levels above 3.5 gm.

per 100 cc. were observed; in both they were still rising at discharge.

Seven out of 7 patients observed before the institution of a high protein diet as part of the therapeutic regimen had lowered albumin levels. In only 2 had the level risen to normal by discharge. In contrast, 11 out of 17 patients treated with high protein diets had reduced albumin values, and in 5 of these the value had returned to normal by discharge.

The serum protein levels were lowest at or just before the clinical peak of the disease. The drop in proteins was influenced by the clinical severity of the disease, the duration of the illness before admission, and the amount of protein taken in the diet.

*Serum bilirubin* values were obtained on 13 patients. In only one patient was the value elevated, and then only to 1.4 mg. per 100 cc., though it remained elevated from the tenth through the thirty-first day of rash. Liver damage was demonstrated in this patient by hippuric acid tests performed on the eleventh and sixteenth days of rash.

Eighteen *bromsulfalein (BSP)* tests were carried out on 14 patients. In 6 instances slight retention of the dye was demonstrated; in 2 cases in which several different tests were done, retention of BSP was the only indication of liver damage. In 3 patients the bromsulfalein test was normal, while the hippuric acid test showed a low excretion. In one other the hippuric acid and BSP tests were in agreement. Usually retention of the dye was noted at about the clinical peak of the disease, or early in convalescence, though in 2 cases dye retention was observed before the clinical peak.

TESTS OF KIDNEY FUNCTION. *Urea clearance* tests were satisfactorily completed on 13 patients. One child showed definite evidence of renal damage, with an excretion of less than

50% of normal; she subsequently died from the disease. In 8 patients the clearance was between 50 and 70% of normal; 3 of these patients were over 40 years of age. Four patients showed unimpaired urea clearance with an excretion of 70% of normal or greater. In 2 instances abnormal urea clearance tests reverted to normal by the time of discharge. The degree of damage could not be correlated with the clinical severity of the disease. The reduction in function usually occurred at or before the clinical peak of the disease, though 3 abnormal tests were observed after the peak.

*Phenolsulphonphthalein (PSP) excretion* tests were satisfactorily completed in 9 patients. All excreted normal amounts of the dye in 2 hours. In all instances a greater amount of dye was excreted in the first specimen than in any other—a fact which further supports the conclusion that the tubular excretory function was not impaired. In 3 patients on whom a urea clearance test was also run, the results indicated a questionable impairment of function.

*Nonprotein nitrogen* levels were determined in all but 7 patients, and were followed serially in 13 patients. In 2 cases the NPN exceeded 70 mg. per 100 cc. before the clinical peak of the disease. In 5 cases the NPN was found to be between 40 and 70 mg. per 100 cc. at some time. In 12 patients the level did not exceed 40 mg. per 100 cc. at any time. In 4 patients an elevated NPN returned to normal by the time of discharge, but in one it was still 44 mg. per 100 cc. In 2 others repeat determinations were not done. Since the fluid and protein intake, blood pressure, urinary output, and renal function all affect the level, it was impossible to correlate the changes with the severity of the illness.

*Albuminuria* of varying degrees was

observed at some time during the course of the illness in 10 patients. Only 2 patients had a frank albuminuria, with a 2 plus reaction; 5 patients showed 1 plus reactions, and 3 patients had a trace of albumin. In most instances albuminuria was found early in the course or at the clinical peak of the disease; it usually persisted for two or three days only, and then disappeared. In 5 patients who had had albuminuria, the reaction was negative by the time of discharge. Since the amount of albumin in the urine is influenced by fever and by the urine volume, it was not possible to correlate the degree of albuminuria with the clinical severity of the disease.

*Microscopic examination* revealed occasional granular or hyaline casts in only 8 cases. One patient had frank hematuria, with numerous red cells in the centrifuged urinary sediment, but the abnormality persisted only one day; a simultaneous determination of the prothrombin time was not done. Four patients had slight hematuria (2 to 5 red blood cells per high power field) for periods of 1 to 3 days. In most instances microscopic abnormalities in the urinary sediment were found at about the clinical peak of the disease; rarely were changes observed during convalescence. No alterations suggestive of acute glomerulonephritis were found at any time.

**Discussion. LIVER FUNCTION.** Disturbances in liver function were observed in patients with Rocky Mountain spotted fever. Alterations were greatest in the conjugation of benzoic to hippuric acid and in the serum levels of albumin and globulin, but changes were also observed in the bromsulphalein retention test, the van den Bergh reaction, and the prothrombin time. The degree of the functional disturbance usually was not marked, but was roughly parallel to the clinical severity of the disease.

Definite alterations were seen even in mild cases. The maximal changes in the prothrombin time and serum protein content occurred at about the clinical peak of the disease. Alteration in hippuric acid excretion was most frequent at the clinical peak, but also occurred during convalescence; no abnormal test was observed early in the course of the disease. Bromsulfalein retention was seen at each period tested. All functions tended to return toward normal as the patient recovered.

Alterations in prothrombin time reflect one function of the liver—synthesis of complex molecules. The prothrombin time is a measure of the prothrombin contained in the circulating blood at the moment; it does not indicate stores. The 2 cases in which marked changes in the prothrombin time occurred were both severe, and in both cases the change appeared overnight. The prompt response of parenteral vitamin K in one case would indicate that liver function was not greatly impaired. The total serum proteins at the time were only 3.9 gm. %. A BSP test performed 6 days previously was normal. The other patient did not respond promptly to parenteral administration of vitamin K, and was so ill that he was not expected to recover<sup>12</sup>. The galactose tolerance and BSP tests were normal at the time; a satisfactory hippuric acid test was not obtained until one week after the prothrombin time reverted to normal at which time 4 gm. was excreted.

Unfortunately, no determinations of the prothrombin time were obtained in 2 of the 3 fatal cases; in the other the time was normal 5 days before death. None of the patients had received salicylates or sulfonamides (which are known to induce liver damage and to prolong the prothrombin time) for several days before

the abnormalities were noted.

A comparison of the prothrombin time and serum albumin level is not possible, because many of the patients received preformed protein intravenously, in the form of whole blood, plasma or purified human albumin, as part of the supportive therapy<sup>11,20</sup>. These measures, as well as the high protein diet, probably would have less direct effect upon the prothrombin time than upon the albumin level.

Hippuric acid excretion was altered in each of 6 patients tested before a high protein diet became part of our therapeutic regimen. After routine treatment with forced feedings of a high protein diet was instituted, the abnormality was observed in only 3 of 18 patients. The fact that the albumin content was decreased in each of 7 patients tested before introduction of the diet, and in only 11 of 17 patients after use of the diet was begun, lends further support to our belief that a high protein diet helps to prevent liver damage. In addition, the diet reduces the amount of preformed protein required for support of the circulation and seems to minimize the development of peripheral circulatory collapse and edema<sup>13</sup>.

*Pathogenesis of liver damage in infectious diseases.* The pathogenesis of the liver damage occurring in Rocky Mountain spotted fever is not clear. Though the rickettsias are characteristically found intranuclearly in the endothelium and smooth muscle cells of arterioles, vascular lesions in the liver are not prominent. In fatal cases small areas of necrosis have been observed in the midzonal areas away from arterioles<sup>31</sup>. In the absence of myocardial failure, the liver was palpable in only one of our patients. In none of the 3 fatal cases was the liver found to be enlarged at autopsy; microscopic examination showed slight degeneration of parenchymal cells with



minimal vacuolization in only 1 patient. This child had marked purpura and was treated before the introduction of the high protein diet. We have not attempted serial aspiration biopsies of the liver to correlate functional and anatomic damage in this disease.

In certain other infections, such as epidemic virus hepatitis, yellow fever, and homologous serum jaundice, hepatic cells apparently are directly parasitized. Hepatitis has been observed following interstitial infections of the liver with bacteria such as the beta hemolytic *Streptococcus* and *Escherichia coli*. In other diseases the reticuloendothelial (Kupffer) cells in the liver become filled with larger intracellular parasites such as the *Leishmania*. In infestations with still larger parasites, such as the *Schistosoma*, the eggs or adult parasites are filtered out in the venous channels of the liver and induce a local foreign body reaction with marked scarring.

Functional liver damage has been observed in many infectious diseases; in few instances, however, have multiple tests been performed to measure different functions, or have tests been run serially. Except when there is direct parasitization of the liver cells or massive extracellular invasion by bacteria, spirochetes or larger parasites, function is seldom altered greatly. Reduction in function may occur during the acute febrile period or during convalescence. It has been noted that alterations develop most frequently about 3 weeks after the onset of any disease. In scarlet fever the changes occur at about the time complications develop, during the third week of illness<sup>2,4</sup>. In malaria the alterations in the cephalin-cholesterol flocculation, albumin-globulin ratio, and bromsulfalein excretion occur during the acute febrile phases of the illness<sup>7,9,24,26</sup>. Indeed, decrease in liver function has

been observed in fever produced artificially without actual infection<sup>1,18</sup>. Studies have also been conducted in patients with chronic infectious arthritis, infectious mononucleosis, experimental infectious hepatitis, pneumococcal pneumonia, lymphogranuloma, and tuberculosis<sup>6,14,16,19,23,29</sup>.

The exact mechanism by which changes in hepatic function occur without destruction or compression of liver parenchyma is obscure. Fever itself apparently will reduce the function of hepatic cells, but the changes quickly disappear as the temperature subsides. This mechanism may explain transient alterations appearing early in the course of a disease. It is possible that soluble products of the rickettsias of Rocky Mountain spotted fever might diffuse out of vascular cells elsewhere in the body and reach the liver through the blood, producing a direct hepatotoxic effect; however, the functional changes, except for those in pigment metabolism, usually occur too late to be due to such a mechanism. The alterations in function which have been observed in various chronic infections or late in the course of other acute infections (during the third week of illness, when convalescence is established) would suggest another mechanism. The immune balance has already been tilted by this time, and it seems late for an antigen-antibody reaction to be at fault, as it may be in the pathogenesis of circulatory failure<sup>13</sup>. Furthermore, hypersensitivity has not been demonstrated in patients with Rocky Mountain spotted fever. On the other hand, allergic liver necrosis has been demonstrated in hypersensitive animals after the injection of egg white<sup>15</sup>. In fatal cases of Rocky Mountain spotted fever microscopic lesions found in various organs resemble those seen in serum sickness—an illness which seems to be due solely to the

interaction of antigens and antibodies<sup>17</sup>.

*Prophylaxis against liver damage.* A prolonged and severe illness reduces the intake of protective foods and exhausts the stores of many body substances. This situation may induce a metabolic imbalance which could duplicate that resulting from the experimental restriction of proteins and lipotropic substances to produce fatty livers<sup>3</sup>. In our experience a high protein diet with vitamin supplements has afforded some protection against liver damage in Rocky Mountain spotted fever. In therapeutic malaria, however, a moderate increase in the protein intake has afforded no protection against alterations in hippuric acid excretion<sup>7</sup>. In experimentally produced burns, where liver damage is known to occur, a high protein diet supplemented with methionine has tended to reduce the extent of protein catabolism as measured by nitrogen loss in the urine<sup>5</sup>. Presumably the liver would also be protected to some extent.

*Measurement of liver damage.* In any event, the defect in liver function occurring in Rocky Mountain spotted fever is not great enough to cause death, and is reparable with recovery. The introduction of effective specific antibiotic therapy with aureomycin and chloromycetin may reduce still further the incidence of abnormal liver function tests in this disease. From our experience we believe that a few selected tests—albumin and globulin levels, prothrombin time, and hippuric acid excretion—done in the second week of rash will detect functional liver damage and provide a good index of its degree. On the basis of the limited data available and the hemorrhagic character of the anatomic lesions, the response of the prothrombin time to parenteral injections of vitamin K may be helpful in estimating prognosis.

*KIDNEY FUNCTION.* Renal function is altered less than liver function in Rocky Mountain spotted fever, but the disturbance does not appear to parallel the clinical severity of the disease. A decrease in kidney function has been observed less frequently than alterations in the liver. Maximum changes appear earlier than with liver damage and seem to revert promptly to normal with recovery. The reduction in kidney function seen in patients past the age of 40 should not be attributed solely to the infection, since the amount of functioning renal tissue is known to be reduced by the ordinary wear and tear of advancing years. The reliability of the urea clearance test as a measure of renal function in children is not universally accepted, but no other tests gave conclusive evidence of renal damage. No changes have been observed which resemble those seen in glomerulonephritis.

In view of the high excretion of urinary nitrogen which occurs in Rocky Mountain spotted fever, as well as in other infectious diseases, and the minimal alterations in urea clearance tests, it is probable that the azotemia which has been observed in many cases is due, not to renal insufficiency, but to massive destruction of proteins or to reduced glomerular filtration caused by circulatory disturbances<sup>8,10,11</sup>. Circulatory disturbances affect renal function more than liver function. The distribution of body fluids, as determined by simultaneous measurements of the blood volume and extravascular thiocyanate fluid space, has been shown to be altered in Rocky Mountain spotted fever<sup>13</sup>.

*Pathogenesis of renal damage.* The mechanism responsible for renal changes is obscure. Fever alone has been known to reduce the creatinine clearance in dogs<sup>27</sup>. In Rocky Mountain spotted fever vascular damage is produced by direct parasitization of

cells. In serum sickness and the experimentally produced vascular disease resembling periarteritis nodosa, renal lesions are pronounced and are accompanied by albuminuria; albuminuria has not been marked in our cases of Rocky Mountain spotted fever<sup>25,28,30</sup>. The time of occurrence of the renal damage does not fit with an antigen-antibody reaction. Such reactions, resulting in serum sickness, have been shown to decrease the excretion of chloride and water; a reduction in blood chlorides and retention of water have been observed frequently in Rocky Mountain spotted fever, but have not yet been shown to be due to a renal defect<sup>10,12,28</sup>.

No specific measures have been devised which will afford protection against the temporary renal damage.

**Summary.** 1. Functional liver damage, roughly related in degree to the clinical severity of the illness, has been demonstrated by us in patients with Rocky Mountain spotted fever. Changes were most marked and most frequent in the hippuric acid excretion test, which usually showed the greatest alteration at or following the clinical peak of the disease. Reduction in pigment metabolism (as measured by the bromsulfalein retention test and the van den Bergh reaction) and reduction of the formation of complex

molecules by the liver (as shown by the prothrombin time and the albumin and globulin contents of serum) were found during the acute febrile phase of the disease. All liver functions returned to normal during convalescence.

2. Functional renal damage was demonstrated occasionally in the course of Rocky Mountain spotted fever. Reduced urea clearance values and transitory albuminuria or hematuria were observed. The azotemia commonly found is probably caused by factors other than reduced renal function. The defect in renal function was slight in degree, occurred before, during or after the clinical peak of the disease, and returned to normal during convalescence; the degree could not be correlated with the clinical severity of the illness.

3. These changes are not specific for Rocky Mountain spotted fever and are not significantly different from those obtained in many other generalized infections.

4. The administration of a high protein diet—by forced feedings of a liquid supplement, if necessary—protects the liver against marked functional damage; it does not alter the function of the kidneys, though it may temporarily overload them.

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# EMBOLIZATION WITH MATERIAL FROM ATHEROMATA

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EMBOLIZATION of systemic arteries with material from eroded aortic atheromata has been recognized only recently as a clear cut histological entity, although it is by no means rare and references to its occurrence can be found in some of the older text books. Flory<sup>5</sup> devoted an excellently illustrated article to this problem, while Meyer<sup>8</sup> from Rössle's Institute, not being aware of Flory's paper, stated in a paper published only 2 years ago that he had discovered a new type of embolization.

The reasons for the delayed discovery of such a basic process are several, the foremost being misinterpretation of the findings as organizing thrombi, as pointed out by Meyer. Yet it remains amazing that lesions of this type are not generally familiar to pathologists.

The following report is a case in point:

**Case Abstracts.** CASE 1. This 62 year old man was admitted because of "ashen color," labored respirations, restlessness and confusion. He had ecchymoses over buttocks and thighs and was bleeding from the rectum. The past history was noncontributory except for an episode of unconsciousness 4 months before this admission which had required hospitalization elsewhere. On admission here he was found to have a hard, large, nodular prostate. He had severe anemia, occult blood in the stool and only 5,000 platelets per c.mm. in the peripheral blood. The differential count suggested diffuse bone marrow replacement. The sternal marrow aspiration revealed tumor cells. Blood urea nitrogen was 107 mg. and

creatinine 4.7 mg. per 100 cc. The urine contained 3+ albumin with a specific gravity of 1.021, 4 to 5 red blood cells per high power field and some granular casts. Despite supportive measures the patient died on the third day in the hospital. The clinical diagnosis was carcinoma of the prostate with widespread metastases.

This was confirmed at autopsy (14130). There was involvement of lymph nodes, lungs, right ureter and vertebral bone marrow with marked osteoplastic reaction. There was severe systemic arteriosclerosis with sclerosis of all the coronary artery branches with minimal narrowing. The myocardium showed focal necrosis which was ascribed to the anemia. Bilateral hydrothorax, pulmonary edema and acute hepatic congestion were present. There was severe atheromatosis of the aortic arch, the thoracic and abdominal aorta, as well as the splenic and left renal arteries. Many of these atheromata were eroded. The iliac veins were not thrombosed. Multiple acute splenic infarcts and healed renal infarcts were found. In the absence of valvular disease, mural thrombi of the heart and patent foramen ovale, it was postulated that the infarcts of spleen and kidneys were due to embolization of atheromatous material from the eroded aorta.

*Microscopic examination of frozen sections* from the infarcted areas of kidney and spleen revealed the vessels supplying these areas to be plugged by amorphous material embedded in which were found acicular spaces. When the Schultz test<sup>14</sup> was applied to these slides the colorless, doubly-refractile material in these slit-like spaces underwent the color changes typical of cholesterol (green in a few minutes and brown in 30 minutes). In addition to spleen and kidney, embolization could be demonstrated microscopically in the arteries of the following organs: pancreas, prostate, thyroid, jejunum, rectum, vertebral marrow, periosteum of the sternum and common

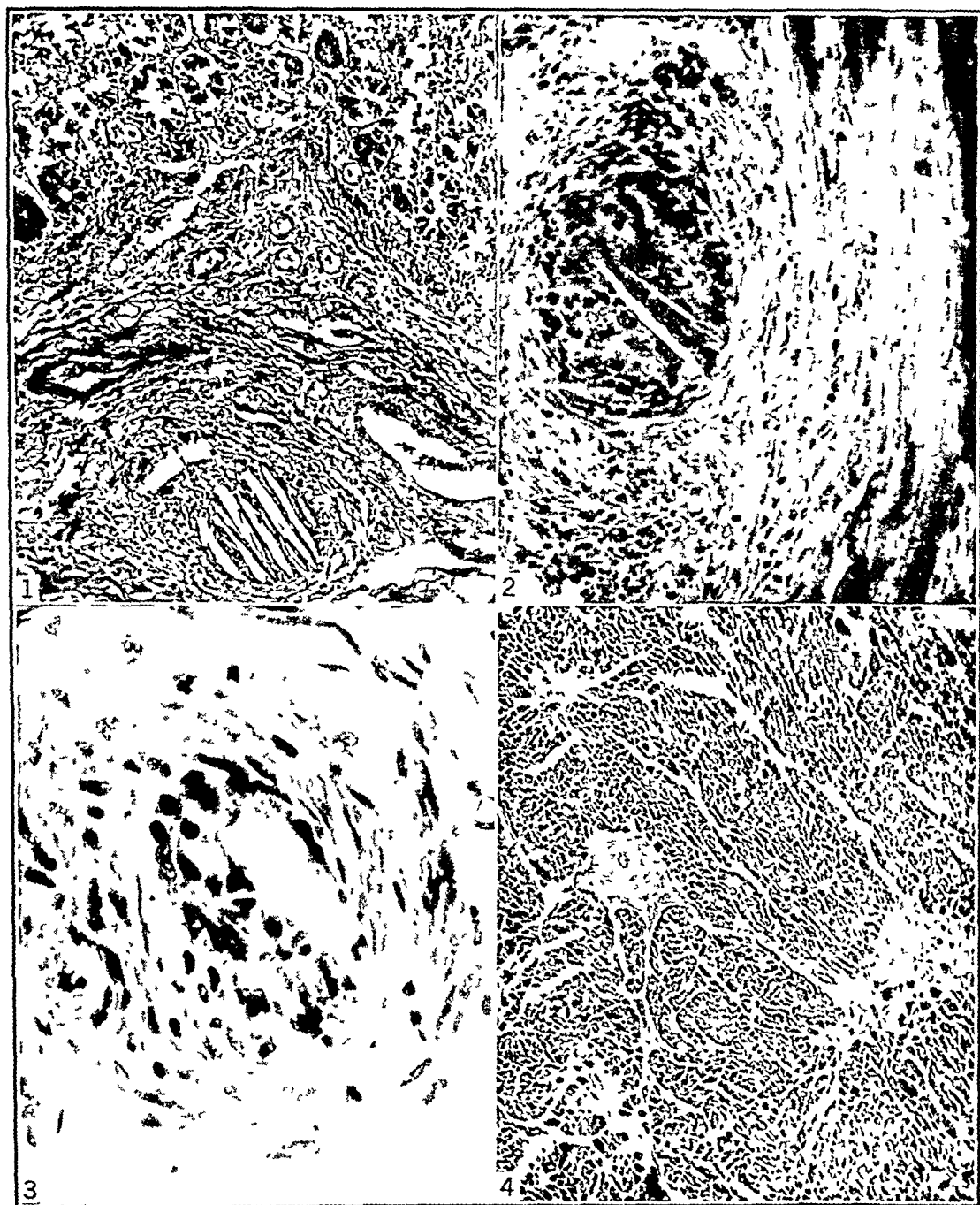


FIG. 1. CASE 1. Large submucosal artery in jejunum, containing acicular spaces in parallel arrangement with giant cell reaction ( $\times 150$ ).

FIG. 2. CASE 2. Acicular spaces and amorphous material in the lumen of intramural coronary artery branch with leukocytic (predominantly eosinophilic) reaction ( $\times 350$ ).

FIG. 3. CASE 2. Intramural coronary artery branch showing fibrous wall with inflammatory cells. Lumen contains similar cells surrounding large eccentrically located fusiform space ( $\times 600$ ).

FIG. 4. CASE 2. Intimal thickening of intramural coronary artery branch with 3 small scars in the surrounding myocardium. Same artery as in Fig. 3, at different level ( $\times 50$ ).

bile duct. Frequently there was typical foreign body giant cell reaction surrounding the intravascular cholesterol crystals.

This case then represents the most common form of atheromatous embolization, namely the chronic or even healed phase of embolization with atheroma material. Some of the involved organs, seen in this case, have either not been mentioned before or pictured as being involved by this type of embolization and it is for this reason that we show an illustration of the jejunum (Fig. 1).

The acute phase of this process appears to have escaped the attention of histopathologists and for this reason the following case is reported:

**CASE 2.** A 35 year old man of Armenian extraction was admitted because of "not feeling well" for several hours. While in the reception room he developed deep cyanosis with stertorous breathing and lapsed into coma. The heart beat and pulse became unobtainable and he died shortly thereafter.

*Autopsy* revealed the following pertinent findings (13563): Severe coronary arteriosclerosis with occlusion of the right coronary artery about 1 cm. from the ostium by a hemorrhagic plug. The heart weighed 375 gm. and was pale reddish-brown and flabby. All cardiac chambers were moderately dilated. Endocardium and valves were normal. There was a lentil-sized greyish patch in the posterior wall of the left ventricle. There was arteriosclerosis of the aorta, particularly of the descending thoracic and abdominal parts. There was no erosion of plaques in the aorta anywhere. *Microscopic study* confirmed the above findings and showed the occlusion of the right coronary artery as being due to hemorrhage into an atheromatous plaque. Acute and subacute myomalacia was found in the posterior wall of the left ventricle.

There was, however, one feature which at first could not be explained properly, namely the occurrence of inflammatory cells, among them many eosinophils, surrounding intramural arteries and extending into the broader septa of the vicinity. This was seen only in the posterior wall of the left ventricle and not in sections from other parts of the heart. A fortuitous frozen section accidentally supplied us with the correct answer (Fig. 2). This section showed arteries within the myocardium, surrounded by a dense inflammatory infiltrate and plugged by amorphous material

containing acicular spaces, usually associated with cholesterol crystals. It was then decided to cut serial sections of the tissue block from the posterior wall of the left ventricle. Our expectations were substantiated as several arteries which at first showed only the inexplicable perivascular inflammation, in the serial sections revealed incontestable proof of occlusion by amorphous material containing slit-like spaces. This can only be interpreted as embolization with atheroma material from the right coronary artery inasmuch as there was no eroded atheroma anywhere in the aorta.

Careful scrutiny of the serial sections allowed chronological grading of the vascular lesions. Vessels surrounded by inflammatory cells with prevalence of polynuclears (and eosinophils) were felt to represent the most acute phase. Lesions where multinucleated giant cells are prominent represent a later stage. The oldest lesion found is characterized by fibrous thickening of the intima (Fig. 3). Lesions of this type were associated with small myocardial scars at a short distance from the occluded vessel. These scars could be traced to arterioles arising from the obstructed artery (Fig. 4).

This case brings up several new points. Firstly, embolization with atheroma material may arise from an artery other than the aorta—in this instance the right coronary artery. Secondly, myocardial scars may be due to this process, a fact which might be brought out by use of serial sections. Thirdly, the acute phase of this condition may impress as an arteritis with conspicuous eosinophilic polymorphonuclears. Whether this is due to an allergic response to the body's own proteins which are present in the atheroma we are not prepared to say.

**CASE 3.** The last case to be discussed concerns a 77 year old woman who was admitted for gangrene of the middle toe of the left foot. She had had pain in both legs for 2 months before admission, and a black spot in the area described was noted 10 days before admission. This spread with increasing pain. She had had a "heart attack" some 5 years before admission, which confined her to bed for several weeks. An electrocardiogram was not taken at the time. On admission she appeared acutely ill with a blood pressure of 120/80 and irregular pulse averaging about 72 beats per minute. She had kyphoscoliosis to the right and dullness at the right base with

diminished breath sounds in the same area. Her heart was enlarged to the left with a systolic murmur and apical gallop rhythm. Radial pulses were poor and so was the left femoral pulse. The patient died on the third hospital day while on penicillin therapy.

*Autopsy* (14159) revealed severe systemic arteriosclerosis. There was an arteriosclerotic occlusion of the superior mesenteric artery

near its origin and an old occlusion of the anterior descending branch of the left coronary artery with a healed infarction of the anterior wall of the left ventricle. The heart weighed 550 gm. The right and left ventricles were dilated and hypertrophied. The mitral ostium admitted 2 fingers and therefore did not participate in the dilatation of the ventricle. This was due to marked thickening and

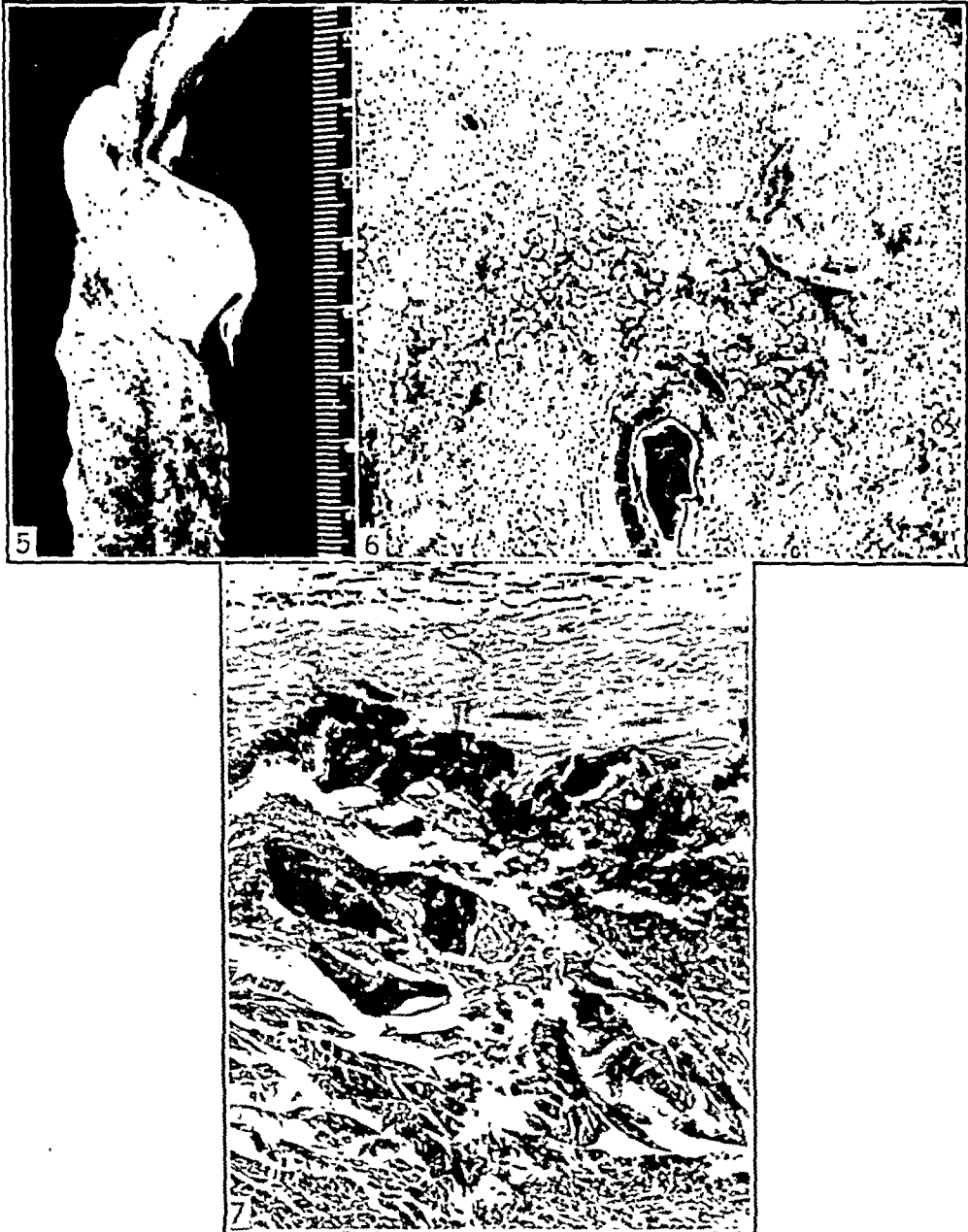


FIG. 5. CASE 3. Cross section through posterior wall of left auricle and ventricle, showing atheromatous mass arising from the mitral valve ring and pushing the posterior cusp into the ventricular lumen.

FIG. 6. CASE 3. Jagged basophilic fragment similar to the ones in the mitral ring atheroma in the wall of a large renal artery, associated with a healed infarct ( $\times 50$ ).

FIG. 7. CASE 3. Microscopic view of the margin of the mitral valve ring showing the fibrocalcific capsule and atheromatous material with large jagged fragments ( $\times 150$ ).



sclerosis of the mitral valve ring, which caused a 15 mm. bulge on the undersurface of the posterior mitral cusp. The lateral margins of this bulging mass fused with the sclerotic mitral ring. On cross section this mass was calcified in the periphery and contained yellowish-white grumous material (Fig. 5). No mural thrombi were found in the heart. The coronary vessels and the aorta showed marked atherosclerosis. No scars were noted in the spleen or pancreas at the time of the gross examination. The kidneys weighed 185 and 210 gm., were reddish-brown and their capsules stripped readily. The exposed surface was finely granular with numerous coarse depressed red scars varying from several millimeters to 1 cm. in diameter. These scars were mainly localized along the convexity of the organ giving the typical appearance of a senile arteriosclerotic kidney.

*Histological examination* however showed a large branch of a renal artery leading into a deep cortical scar to be almost occluded by a basophilic, jagged fragment the nature of which could not be ascertained at first (Fig. 6). Similar fragments were seen in other branches of the renal artery and in arteries of the pancreas and spleen. Invariably the fragments were embedded within the arterial wall and separated from the lumen by a layer of intima of variable thickness. This was observed in serial sections and presented also an unexpected finding. Occasionally these jagged fragments were eosinophilic.

*Microscopic study* of the section of the mitral valve ring clarified the nature and probable origin of the aforementioned fragments. The large atheromatous thickening of the valve ring contained fragments which were identical in size, shape and staining characteristics with the ones found in kidney, spleen and pancreas (Fig. 7). It was then decided that the lesions in kidney, spleen and pancreas were of an embolic nature. Although similar fragments may be found in aortic atheromata, the absence of the cholesterol crystals in the embolic lesions and in the mitral valve ring lesion speak against an aortic origin of the embolic material.

Closer scrutiny of the mitral ring lesion shows how attenuated the tissue is in places. One can well imagine that a lesion of this unusual size may thus perforate and empty some of its contents into the systemic circulation. The peculiar position of the embolic material within the wall of the arteries and separated from the lumen is, in our opinion, due to the lesion being healed after embolic material has become impacted in the wall, a process which in other instances led to the formation of aneurysms; for example, in healed subacute bacterial endocarditis<sup>6</sup>.

This patient then represents a case of embolization with material from an unusually large arteriosclerotic valve ring. To our knowledge no similar case has been reported. The gangrenous toe could not be examined microscopically and might have been of embolic origin, although this is not too likely because of absence of acute embolic lesions in other organs.

*Discussion.* Panum<sup>9</sup>, in a study on embolism, reported the gross findings of the autopsy of Thorwaldsen and ascribed his sudden death to atheromatous rupture in the coronary artery with occlusion due to this rupture. No microscopic examination is recorded.

Doch<sup>1</sup> reported a case of ruptured coronary atheroma with multiple emboli in the larger coronary branches due to cholesterol. There is no microscopic description of the lesions.

Le Count<sup>7</sup> describes calcareous emboli of several organs and the heart and traces these emboli back to atheromata.

Allbutt<sup>1</sup> also mentioned the possibility of embolization from atheromatous ulcers into various organs, making special reference to syphilitic arteritis.

Benson<sup>2</sup> reviewed the literature of aortic atheromata giving rise to emboli and comes to the conclusion that there is reason to believe that they are more common than had been realized.

Flory<sup>5</sup> is the first to describe in detail the microscopic lesions and interpret them as cholesterol emboli. He found these in the lumina of arteries of the kidney, spleen, pancreas and thyroid. Foreign body giant cells partly surround the acicular spaces. Flory found these lesions in arteries from 55 to 900 $\mu$  in external diameter. In these lesions the intima was found to be hyperplastic and giant cells are an almost constant associated finding. Occasionally there were hemosiderin-filled macrophages found in the luminal occlusion, suggesting an organizing embolus or previous hemorrhage. To confirm the impression that these lesions were embolic, origi-

nating in aortic atheromata, this author scraped yellow material from several fresh aortic plaques and suspended the scrapings in physiologic saline solution. Microscopically, this suspension contained cholesterol crystals, fat droplets and red blood cells. This material was injected into the ear veins of 2 rabbits, and lesions similar to the ones described above were found in the small arteries of the lungs, surrounded by leukocytes if the animal was sacrificed 24 hours after injection, and surrounded by foreign body giant cells and hyperplastic intima when sacrificed 7 days after injection. In a review of autopsy material of 267 subjects likely to have similar lesions, he found an incidence of 3.4%. Excellent illustrations are included in this paper.

Meyer<sup>8</sup> described in detail 2 cases of cholesterol embolization. One case showed numerous lesions in the kidneys and in the pia-arachnoid, presumably arising from aortic atheromata superimposed on a syphilitic aortitis. The other case showed numerous lesions in the kidneys, spleen, brain, gastrointestinal tract and some in the myocardial arteries in the presence of moderately severe ulcerating atheromatosis of the aorta. The lesions he describes and illustrates are essentially similar to those described by Flory.

The findings in our 3 cases represent various aspects—some of them new—of embolization with material from athero-

roma. Their special features were discussed above.

**Summary.** 1. Embolization with atheromatous material is far more frequent than generally assumed. The pathologist usually sees the late or healed form which was described recently by Flory and independently by Meyer. Our first case belongs to this group.

2. The embolic material does not necessarily come from aortic atheroma but may occasionally arise in a systemic artery (coronary artery, Case 2) or even in an atheromatous valve ring (Case 3).

3. The acute phase of this process may represent itself as a panarteritis with many eosinophils, necessitating serial sections for elucidation of its true nature (Case 2). Foreign body giant cell formation and intimal thickening are later phases of this process.

4. Scars, *e.g.*, in the kidneys, may be caused by these emboli and microscopic scarring of the myocardium likewise.

5. Embolization with atheroma material should be regarded by the clinician as an existing and not too rare entity. Pathologists and neuropathologists should prove its presence in any given case. It is possible that a good number of cases of cerebral damage may be caused by this type of embolization, as may be transient and permanent impairment of visceral or peripheral circulation (toes, and so on).

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# THE OCCURRENCE OF CHRONIC CYANOSIS IN CASES OF ATRIAL SEPTAL DEFECT

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ROESLER<sup>20</sup>, Bedford, Pap and Parkinson<sup>4</sup>, and Burrett and White<sup>6</sup> presented excellent reviews of clinical and pathologic features of atrial septal defect, which is thus one of the best known syndromes in congenital heart disease. Atrial septal defect was classified by Abbott<sup>1</sup> and others as a late cyanotic lesion, one associated with "cyanose tardive"<sup>3</sup>, terminal cyanosis due to a reversal of the direction of the intracardiac shunt which occurs with cardiac failure increasing pressure in the right auricle. Taussig<sup>23</sup> stated recently that slight acrocyanosis due to diminished blood volume and increased utilization of oxygen in the body may be present in atrial septal defect, but "there is . . . never the intense cyanosis and concomitant clubbing which are so characteristic of a venous-arterial shunt". She states that if clubbing is present it is indicative of some additional factor.

Recent studies of arterial oxygen saturation in cases of atrial septal defect<sup>5,11,14,25</sup> have demonstrated varying degrees of arterial anoxemia in patients who apparently were not in cardiac failure. We were provided with the opportunity of observing a patient who showed chronic cyanosis, polycythemia and clubbing of digits and who at autopsy was found to have an uncomplicated atrial septal defect. The purpose of this communication is to

report this case, to review autopsied cases of atrial septal defect collected from the literature in which chronic cyanosis was observed and to discuss the possible causes of cyanosis associated with this lesion.

**Case report.** A 35 year old college instructor entered Stanford University Hospitals for a diagnostic checkup on May 21, 1947.

He was born at term and was not a "blue baby". Except for a slight tendency to breathlessness, his development was normal. At the age of 12, after a foot race he suddenly became extremely dyspneic and consulted a physician who told him he had a "leaky valve" and restricted his activities. At the age of 24 he developed attacks of squeezing precordial pain of 1 to 2 hours duration usually related to emotional upsets. He was not reported then as being definitely cyanotic. In his late twenties he developed clubbing of fingers. He was in reasonably good health and was moderately active, suffering from exertional dyspnea and attacks of precordial pain which were relieved by nitroglycerin. His hospitalization was prompted by a desire to find out whether his cardiac disease was correctible by surgery.

**Physical examination** revealed a tall, well nourished and developed man who showed moderate cyanosis. His heart was slightly enlarged to the left. There was a diastolic shock felt. A loud second sound was heard over the pulmonic area, but otherwise no abnormal auscultatory findings were reported. After exercise there was a grade I blowing apical systolic murmur. Fingers and toes showed marked clubbing and cyanosis of the nail beds. His blood pressure was normal.

**Laboratory procedures.** Blood count: Hgb. 20.7 gm., rbc. 7.2 mil., packed cell volume, 58%, otherwise normal findings. Urinalysis

not remarkable. Circulation time (arm to tongue) 21 secs.; venous pressure, 7 cm. water; vital capacity, 3.4 liters. A 4 lead electrocardiogram showed right-axis deviation with diphasic T-waves in Leads 2 and 3. Oxygen saturation of venous blood was determined after immersion of the hand in warm

water to approximate arterial oxygen saturation and a value of 44% was obtained.

*Roentgen-ray studies.* Chest roentgenograms revealed a striking prominence in the region of the pulmonary artery and its branches with widening of the upper mediastinal shadow, but only a moderate cardiac enlargement

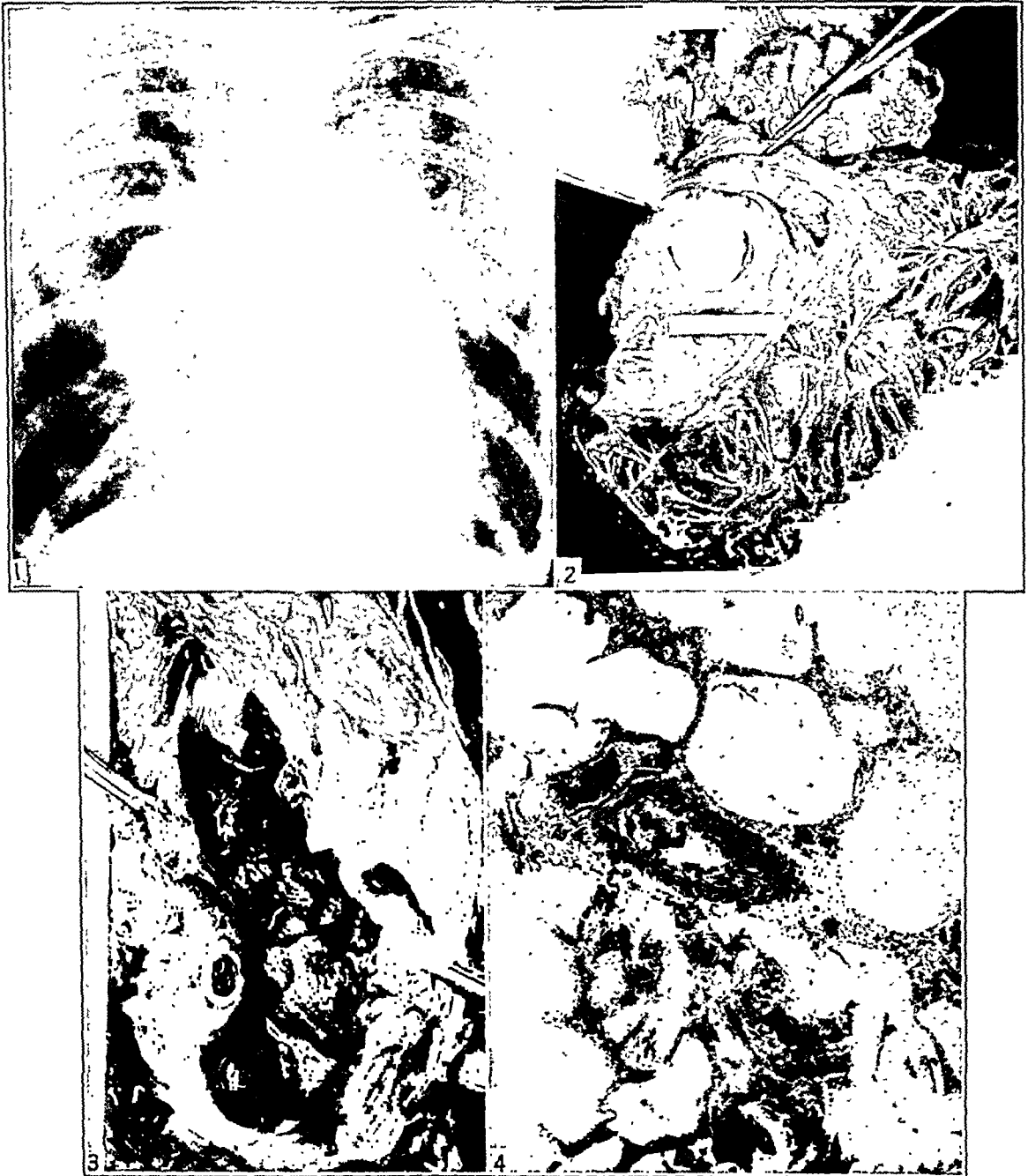


Fig. 1. Roentgenogram of chest.

Fig. 2. Right ventricle and auricle, showing hypertrophy and dilatation of the right ventricle, dilatation of the right auricle and the defect in the atrial septum.

Fig. 3. The aneurysmal sac of the left branch of the pulmonary artery, lined with thrombi.

Fig. 4. A section through the lungs showing a representative small branch of the pulmonary artery: slight medial hypertrophy and intimal thickening but no proliferative changes.

(Fig. 1). The pulsations of the pulmonary artery segment were not considered abnormal.

*Course.* The patient was discharged after a week's stay in the hospital and he returned to work. In December of 1947 he was examined in the out-patient clinic, and his condition was reported essentially unchanged except that a definite systolic murmur was heard along the left sternal border and his packed cell volume was 61%.

The patient was readmitted on June 7, 1948, stating that 2 days previously he had developed anterior chest pain and had had repeated small hemoptyses. Immediately after admission he complained of increasing chest pain, began expectorating blood, went into shock and died 1 hour after admission.

*Autopsy.* At post-mortem examination clubbing of the fingers and toes was noted. There was marked lividity of the dependent parts but no ankle or sacral edema. When the thorax was opened approximately 1 liter of clotted and liquid blood was found in the left cavity, while the right side was almost dry. The pericardial space was obliterated by diffuse fibrous adhesions. The heart, emptied of blood, weighed 525 gm. The right atrium was voluminous and almost continuous with the small left atrium through a defect about 4 cm. in diameter (Fig. 2). The remnants of the interatrial septum were represented by a blunt low ridge of tissues on the inferior margin of the defect, lying near the midline above the interventricular septum. The right ventricle had thick trabeculations; its wall was about 5 mm. thick and its chamber appeared to have about twice the volume of that of the left ventricle which was 8 mm. thick. The pulmonary valve leaflets were normal but the circumference of the valve was 11.5 cm. The following additional measurements of valve circumference were obtained; tricuspid 15 cm., mitral 12 cm., aortic 9 cm. The coronary vessels were open and free of sclerosis. The pulmonary artery and its left primary branch had a large aneurysmal dilatation about 10 cm. in diameter partially filled with layers of thrombus (Fig. 3). At the distal margin of this aneurysm there was a tear opening upon a large friable mass of clotted blood which replaced much of the pulmonary parenchyma of the left lung. This mass extended out into the pleural space through a tear in the pleura near the base. There was some old dense, white scar tissue in the region of this tear. The right primary branch was dilated but contained scattered atheromatous plaques in its wall. The left lung, which was filled with blood, weighed 700 gm.; it showed little crepitation and with pressure its cut surface exuded large quantities of blood. The trachea and both bronchi

contained some clotted and fluid blood. The remaining viscera were not remarkable.

*Microscopic examination.* There was some thickening of the myocardial fibers of the right ventricle and the epicardial fat was replaced by loose fibrous tissue in all sections. In sections of the aneurysm the clot was composed of concentric laminae of thrombus in various stages of hyalinization. There were capillary ingrowths and numerous leukocytes in portions of the thrombus near the wall. The adjacent vessel wall was flattened and contained occasional prominent strands of collagen among the elastic fibers of the media. In the region of the rupture the fibers of the wall were fragmented and the adventitia was heavily infiltrated with leukocytes. Sections of the right pulmonary artery revealed some atheromatous thickening in the vessel walls. The pulmonary parenchyma adjacent to the tear was almost obliterated by recent hemorrhage and the more distant alveoli were filled with blood. Scattered throughout both lungs were occasional areas of old and recent focal hemorrhage. In some of the foci the parenchyma was replaced by granulation tissue containing many macrophages filled with hemosiderin. There were also a few areas with dense bands of fibrous tissue containing clusters of hemosiderin-filled macrophages. In sections of the grossly noted thickened pleura there was dense fibrous tissue containing a few aggregates of lymphocytes and occasional leukocytes. The small arteries and arterioles of the lungs were carefully inspected and showed slight intimal thickening (Fig. 4). No thrombi were found.

*Comment.* This is an instance of congenital heart disease with atrial septal defect in which the dilatation of the pulmonary artery assumed aneurysmal proportions and the vessel finally ruptured. Pulmonary artery aneurysms occur not infrequently in association with atrial septal defects and other lesions causing large arteriovenous blood shunts, but rupture of such aneurysms is very rare.

Clinically, this patient fulfilled most of the criteria for the diagnosis of atrial septal defect except for the occurrence of chronic cyanosis, clubbing of digits and polycythemia. These features appear to have developed during the last 10 years of life and were progressive. At no time was there any evidence

of cardiac failure, and the patient was moderately active until shortly before his death.

Pathologic features of this case were in accord with the concept of a sizable left-to-right blood shunt: dilated right auricle and a small left auricle; hypertrophy and dilatation of the right ventricle but none of the left ventricle; finally dilatation of the pulmonary artery. It is noteworthy, however, that although there were atheromatous changes in large pulmonary vessels, there were none of the obliterative changes in the small pulmonary arteries and arterioles usually associated with chronic pulmonary hypertension.

**Cases collected from the literature.** A group of 180 cases of proven atrial septal defect with or without concomitant mitral stenosis (Lutembacher syndrome) were reviewed. These were taken from the following sources: Abbott's<sup>1</sup> chart contained 73 such cases; Roesler's<sup>20</sup> review presented 62 cases, 37 of which were not duplicates of Abbott's cases. McGinn and White<sup>17</sup> reviewed 24 cases of the Lutembacher syndrome, and 7 of these were not included in previously named series. Burdett and White<sup>6</sup> presented a review of 31 recent cases. Welch and Kinney<sup>28</sup> 25 cases, and Dry<sup>12</sup> 4 cases. Three other case reports were used<sup>18,21,26</sup>. Of these 180 cases, 11 were thought to represent atrial septal defect with chronic cyanosis. These cases were accepted in the presence of a history or observation of longstanding cyanosis and one or both of objective confirmatory signs: clubbing and polycythemia. The pertinent pathologic findings in these 11 cases and in our case are presented in Table 1.

It is shown that cyanosis was present since birth in 2 cases and in the majority of others it appeared in the second decade of life. Cyanosis was described in most cases as moderate, in some as severe. Clubbing was present in all

cases except one. Polycythemia was reported in 7 of the 8 cases in which blood counts were recorded. Eight patients died of heart failure, 3 from other causes.

The heart was reported as enlarged in all but one case. In most cases severe hypertrophy was present, usually limited to the right ventricle. The defects varied from moderate sized ones to an almost complete absence of the atrial septum. In 2 cases multiple defects were reported. There was no uniformity in the location of the defects. Some were reported as widely patent foramen ovale, others as persistent foramen primum. In cases with very large defects, identifying landmarks in the atrial septum were obliterated. In 11 cases description of the pulmonary artery was available: it was reported as small in 1, normal sized in 3, moderately dilated in 2 and of aneurysmal proportions in 5. Complicating mitral stenosis, apparently rheumatic in origin, was recorded in 3 cases. In 1 of them the degree of mitral stenosis was probably severe enough to have affected hemodynamics, in the other 2 it was mild.

The sex incidence in this series was: males 8, females 4. The youngest patient was 16, the oldest 44 years of age.

**Discussion.** It is shown beyond any doubt that cyanosis not related to cardiac failure may occur in cases of atrial septal defect with or without complicating mitral stenosis. The degree of cyanosis and of the accompanying polycythemia and clubbing, and the age of their onset, places some of these cases very definitely in the cyanotic group of congenital heart disease. They constitute only a small fraction of the total number: 7% of the reported cases exhibited definite chronic cyanosis.

The fact that atrial septal defect may take the form of morbus caeruleus introduces a new problem in the differ-

TABLE 1.--FINDINGS IN 12 CASES OF ATRIAL SEPTAL DEFECT WITH CHRONIC CYANOSIS

| Author, year    | Age, sex | Cyanosis                     | Clubbing           | Polycythemia | Cause of death                | Heart weight (grams) | Atrial septal defect:   | Pulm Art.:               | R.V.: | Other findings   |
|-----------------|----------|------------------------------|--------------------|--------------|-------------------------------|----------------------|---|--------------------------|-------|--|
| Johnson 1878    | 35 M     | since birth +++              | ++                 |              |                               | 600 gm.              | open F.O., 4-5 cm diam.   | norm. size               | +++   |  |
| Sundberg 1905   | 22 M     | since adolescence ++         | +                  |              | heart failure                 |                      | 2 defects, large poster., small anterior                        | dilated                  | +++   | small aorta  |
| Cabot 1926      | 21 F     | 7 1/2 years duration ++      | +                  |              | heart failure                 | 665 gm.              | widely open F.O. (1 1/2 cm diam.) ant. defect, 1 cm.            | dilated 2x size of aorta | ++    | small aorta mild mitral stenosis                       |
| Zadoc-Kahn 1926 | 30 M     | for at least 2 years +++     | since childhood ++ | +            | heart failure                 | 450 gm.              | atrial septum almost completely absent                          |                          |       |  |
| Wahl 1931       | 21 F     | at 17 + later ++             | +                  | +            | operation                     | 625 gm.              | widely open F.O. 22 mm in diam.                                 | aneurysmal               | +++   | small aorta  |
| Oskeles 1932    | 31 M     | since 16 ++                  | +                  | ++           | heart failure                 | 775 gm.              | fossa ovalis perforated by mult. defects, total size 2 cm diam. | aneurysmal dilatation    | +     |  |
| Costa 1931      | 16 F     | since 14 ++ terminally +++   | +                  |              | heart failure                 | large                | poster. to F.O. mult. holes, 1 cm; 1x2 cm and 4 mm in diam.     | small                    | +     |  |
| Bedford 1941    | 44 M     | since 25 ++                  | ++                 | +            | heart failure                 | large                | F.O. closed, below it oval defect 2x3.5 cm                      | aneurysmal dilatation    | +++   |  |
| Bedford 1941    | 33 M     | since birth +++              | ++                 | ++           | heart failure                 | 930 gm               | large aperture in position of F.O. 2x3 cm.                      | normal                   | +     | mitral stenosis, calcar., severe                       |
| Massee 1947     | 39 M     | ++                           |                    | +            | heart failure                 | 640 gm.              | F.O. closed, open septum primum 5x5 cm                          | twice normal size        | +++   | fibrosis of mitral & tricus. valves; mild mitral sten. |
| Gates 1947      | 39 F     | cyanotic at 19 +++           | ++                 |              | cereb abcess                  | 310 gm.              | widely open F.O. 3 x 2.5 cm                                     |                          | ++    |  |
| Authora case    | 36 M     | developed in mid-twenties ++ | ++                 | ++           | rupture of pulm.art. aneurysm | 525 gm.              | large defect (4 cc diam.) most of atrial septum absent          | aneurysmal dilatation    | ++    |  |

LEGEND.

R.V. = right ventricle, F.O. = foramen ovale, + = slight, ++ = moderate, +++ = severe (in column "R.V." degree of hypertrophy)

ential diagnosis of congenital heart disease. Our case illustrates the similarity between the Eisenmenger complex and the cyanotic form of atrial septal defect. In both of these conditions roentgenographic and electrocardiographic findings are identical, and even physical findings bear a close resemblance in that systolic murmurs located in the apical area and the lower left sternal border occur in both syndromes, and early diastolic pulmonary murmurs may be present in either case. With cyanosis, moderate in degree, appearing in late childhood, differential diagnosis between the Eisenmenger complex and the atrial septal defects may be impossible by ordinary means and may have to rest entirely upon the result of venous catheterization of the heart.

In addition to the diagnostic difficulty this problem calls for an answer to a fundamental question, which we shall attempt to discuss: Is cyanosis associated with atrial septal defect due to the congenital defect itself, or to complicating and secondary factors?

Since Lundgaard and VanSlyke's<sup>10</sup> studies and Abbott's<sup>1</sup> application of their principles to congenital heart disease, venous arterial blood shunt was regarded as the main cause of chronic cyanosis in congenital morbus caeruleus. In the recent years another mechanism has been suggested in some cases of congenital heart disease: Burwell<sup>7</sup> and then Taussig and Blalock<sup>24</sup> thought that in the Eisenmenger complex incomplete oxygenation of the blood in the lungs may be responsible for arterial anoxemia. Brannon, Weens and Warren<sup>5</sup>, and Massee<sup>18</sup> thought that obstructive pulmonary disease and difficulty in oxygen diffusion in the lungs were responsible for arterial anoxemia in their case of atrial septal defect associated with cyanosis. This was based on the fact that in it the right ventricular and pulmonary arterial

pressures were very high and arterial oxygen saturation rose in response to breathing of pure oxygen. In another case of atrial septal defect (not autopsied) Handelsman *et al.*<sup>14</sup> found lowered arterial oxygen saturation and high pulmonary arterial pressure, but interpreted their findings as indicative of a predominant right-to-left intracardiac shunt due to increased resistance of the pulmonary vascular tree. Taylor *et al.*<sup>25</sup> studied a group of patients with atrial septal defects clinically with the aid of venous catheterization of the heart and found occasional subnormal values of arterial oxygen saturation. These authors explain it on a basis of venous-arterial blood shunt, which, they think, may occur in a very large defect, where the 2 auricles form a common chamber.

Thus, 3 ways have been suggested in which arterial oxygen saturation could be lowered in cases of atrial septal defect. Two of them necessitate the presence of a complicating factor: pulmonary vascular sclerosis or pulmonary hypertension; the third one calls for the presence of a very large defect.

Reviewing the pathologic findings in cases of atrial septal defects with cyanosis (Table 1) and the physiologic data accumulated in the last few years by catheter studies, one can confidently dismiss the possibility that pulmonary oxygen exchange is interfered with in all such cases. Pulmonary vascular sclerosis was not a consistent finding in cyanotic cases. In our case it was specifically searched for and found not to be present. In addition, no proof has been offered that pulmonary vascular changes per se, without changes in the lungs, impede oxygen exchange. The conclusive evidence has been provided by successful determinations of the oxygen saturation of pulmonary venous blood which was found to be normal: Handelsman *et al.* reported that in 16



cases the pulmonary vein was catheterized and the blood was fully saturated with oxygen. Details were not given and it is not known whether some of these cases were cyanotic. More significant are cases reported by Dexter *et al.*<sup>11</sup> and Taylor *et al.*<sup>25</sup>, each of whom reported 1 case in which arterial anoxemia was present but the blood returning from the lungs was fully saturated with oxygen. Until and unless conclusive evidence is presented that pulmonary venous blood may be anoxic, pulmonary factors in the production of cyanosis in atrial septal defects can be dismissed and intracardiac shunt can be taken to be the sole cause of anoxemia.

The second possibility, that pressure relationships cause a predominantly right-to-left interauricular shunt, does not fit in with the clinical facts and the postmortem findings. Handelsman *et al.*<sup>14</sup> based their views on a clinically studied case in which the calculated systemic flow was 4 times larger than the pulmonary blood flow. If these calculations were correct, this case would most likely be an exception rather than an average case, as the intense pulmonary congestion usually noted during life, the postmortem findings of a large right auricle, the small left auricle, the dilatation of the right ventricle and pulmonary artery, the small aorta are all incompatible with a large systemic and small pulmonary blood flow. Also, similar calculations by other authors<sup>11,25</sup> have shown the systemic flow to be smaller than the pulmonary flow even in the presence of arterial anoxemia.

Clinical and pathologic findings in cases of atrial septal defect with chronic cyanosis show the same indirect evidence of a large venous-arterial blood shunt as in cases without cyanosis. Such findings speak strongly against the possibility that pulmonary arterial sclerosis or other factors lead to a permanent overall right-to-left shunt in cyanotic

cases. In cases of atrial septal defect the pressure in the left auricle is higher than in the right<sup>10</sup>. It is not known whether this relationship is reversed in the presence of high right ventricular pressure unless right ventricular failure with diastolic hypertension ensues. It should be noted that in the Lutembacher syndrome, the addition of mitral stenosis would accentuate the left-to-right shunt, and yet chronic cyanosis may occur in such cases as well as in uncomplicated atrial septal defects. All these arguments make a change in pressure relationship between the auricles and a resulting permanent overall right-to-left shunt very unlikely.

The possibility of free mixture of venous and arterial blood in cases where both auricles would form a single functional chamber seems to offer the best explanation for cyanosis associated with very large atrial septal defects. In such a case venous blood from the systemic circulation and fully oxygenated pulmonary venous blood could mix freely and the oxygen saturation of this mixture would lie between the values of the arterial and the venous blood. This mixed blood would then flow into both ventricles and gravity<sup>26</sup> or higher pressure on the left side could force more of it into the right heart than the left, causing unequal outputs of the 2 ventricles. The free mixing of blood in a single auricle could, but need not, take place in every case since most of the blood could follow the normal direction even with an absent septum, and mixing could be minimal.

Free mixing of blood in cases of a complete or almost complete absence of the atrial septum offers an explanation of cyanosis consistent with cardiodynamics on one hand and with the pathologic relationship of the ventricles and great vessels as found in these cases on the other hand. A disturbing fact, however, is that in this series

there is no uniformity in the presence of very large septal defects: only one case was actually reported as a "trilocular heart"<sup>20</sup> with a single auricle, and of the remainder, our case and 3 others could be regarded as very large defects. The rest should be classified as moderate sized defects, single or multiple. One is impressed by the fact that the gross pathologic findings in the 12 cyanotic cases, especially the size and location of the defects, present a good cross section of the 180 cases of atrial septal defect.

Another possible mechanism of cyanosis has occurred to us, namely a directional flow of venous blood into the left auricle. If proper anatomic conditions existed, namely a certain relationship of one of the venae cavae to the septal defect, one could visualize a stream of blood thrown directly into the left auricle during the part of the cycle when pressure differences between auricles are smallest. This need not interfere with the large left-to-right shunt during the remainder of the cardiac cycle. The occurrence of such streamlining of blood in the fetal circulation has recently been reaffirmed<sup>2</sup>: in the fetus such a mechanism causes the reverse, namely oxygenated blood from the placenta arriving through the inferior vena cava is shunted directly into the greater circulation.

The possibility of a streamline blood shunt in atrial septal defect is speculative but attractive, as it would best explain apparent inconsistency between the presence of venous blood in the greater circulation and a large left-to-right interauricular blood shunt in cases where free mixture would not appear likely because of the modest size of the opening. Since such a mechanism would be caused by an anatomic chance it would explain the occurrence of cyanosis in some cases and its absence in others, and the lack of correlation between the presence of chronic

cyanosis and the gross anatomic findings.

Since cyanosis, clubbing and polycythemia are clinical manifestations of higher degrees of arterial anoxemia, one might ask whether arterial anoxemia insufficient to cause visible cyanosis is a common or constant feature of atrial septal defect. The answer is provided in the reports of arterial oxygen saturation values in cases diagnosed by venous catheterization of the heart. Such readings are reported in 17 cases<sup>5,11,14,25</sup>: in 5, normal values were found (saturation of 95% or more); in 9, minimal anoxemia was present (values between 88% and 95%), and 3 patients had definitely anoxic values: 79%, 70%, and 67% respectively. These findings indicate that small quantities of venous blood frequently enter the left auricle, and in a small proportion of cases large quantities find their way into the greater circulation.

**Summary and Conclusions.** 1. A case is presented of a large atrial septal defect in a 35 year old man who showed the triad of chronic cyanosis, polycythemia and clubbing of the digits, and who died of rupture of an aneurysm of the pulmonary artery without ever exhibiting evidence of cardiac failure.

2. A review of 180 proven cases of atrial septal defects with or without concomitant mitral stenosis reported in the literature showed that in 11 patients persistent and longstanding cyanosis not associated with cardiac failure was present.

3. Pathologic findings in these cases did not differ from those in other, non-cyanotic cases. Large defects involving most of the atrial septum were common among cyanotic cases but there was no apparent relationship between the size of the defect and the presence of cyanosis.

4. The pathogenesis of cyanosis

associated with atrial septal defects is discussed. Deficient pulmonary oxygenation is not regarded as a likely factor in the production of cyanosis, nor is a changed pressure relationship in the auricles leading to a persistent venous-arterial blood shunt. With the clinical and pathologic evidence pointing to a

large volume of blood being shunted from the left to the right auricle, the most likely cause of cyanosis appears to be a free mixing of blood in very large septal defects and, or, anatomic conditions permitting a stream of venous blood from the great veins to enter the left auricle directly.

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## A STUDY OF 22 CASES OF CARRION'S DISEASE WITH INTERCURRENT MALARIA\*

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IN the last century before the etiologic agents of malaria and Carrion's disease were known, many interesting associations were noted between the 2 diseases. In 1887 Tupper<sup>15</sup> found that *Verruga Peruviana* was present in an area where malaria was also endemic and unfortunately many persons contracted both diseases. Carrion<sup>8</sup> noted that the geographical distribution was similar but pointed out that malaria and *Verruga Peruviana* occur independently of each other but can co-exist in the same person. Dounon<sup>3</sup> concluded that the 2 diseases had a similar pathogenesis and Odriozola<sup>11</sup> found that similar conditions were necessary for the life of the etiologic agents in these diseases. Garcia-Merino<sup>4</sup> correlated the presence of flood waters with the onset of epidemics of Carrion's disease. Today it is known that both diseases are transmitted by mosquitoes: malaria by *Anopheles* and Carrion's disease by the phlebotomus<sup>6</sup>.

The present report is a study of the relationship between Carrion's disease and malaria, as observed in a group of 22 cases found to have both diseases.

Malaria parasites were found in smears of the peripheral blood in all of the 22 cases of this series. The type of plasmodia were: *P. vivax* in 18, *P. falciparum* in 2, and *P. malariae* in 2 cases. In 3 patients the malaria parasites were demonstrated in the peripheral blood following *Bartonella bacilliformis* anemia, hereafter, B.b.a. (Oro-

ya Fever), in another 3 during the pre-eruptive stage, and in 16 during the eruptive stage of the bartonellosis with verrugae in the skin.

Malaria and Carrion's disease may be contracted at the same time or one may precede the other. Patients with severe B.b.a. which were followed by malaria showed clinical features which were atypical for both diseases. The fever was irregular and without the characteristic periodicity of malaria, there was profuse sweating, enlargement of the spleen, and frequently a macrocytic or normocytic normochromic anemia with monocytosis varying from 8 to 20%. These symptoms and signs do not occur in uncomplicated cases of B.b.a.

When malaria was contracted during the eruptive phase of the verrugae, the malarial seizures were usually typical and easily recognizable with chills, high fever and sweating occurring periodically every day, or every second or third day. The morphological aspect of the verrugae changed rather suddenly, they lost their turgescient appearance and disappeared rapidly. Other verrugae assumed a dark violaceous color from thrombosis or hemorrhage. The pains in the bones and joints which were usually present during the pre-eruptive stage and disappeared with the eruption of verrugae again reappeared. The hematological findings in cases with malaria during the eruptive stage of Carrion's disease were quite

\* This study was made in Lima, Peru, from 1938-1943 at five different hospitals: Dos de Mayo, Arzobispo Loaiza, San Bartolome, Del Nino, and Maternidad.

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typical of malaria without any features of B.b.a. In this series of 22 cases with both diseases, monocytosis was found in every one and splenomegaly in 20 cases (91%).

**Report of Cases.** The following 2 cases illustrate malarial seizures during the eruptive stage of Carrion's disease.

**CASE 1.** E. R., a 28 year old, single, Peruvian soldier, had malaria for many years with the last seizure in 1935. In February of 1941 he was sent to an area where Carrion's disease is endemic. In the 3rd week of February he developed malaise with a fever fluctuating between 38° and 39° C., anemia and slight icterus of the skin and sclera, dizziness, cramps in the epigastrium, nausea and occasional vomiting. In the first week of March the fever gradually disappeared, his appetite improved and for the first time he experienced pain in the various bones and joints. This episode apparently corresponded to a B.b.a. On March 19th the patient experienced a chill followed by a fever lasting a few hours, profuse sweating and vomiting. This symptomatology recurred twice every other day at the same hour of the day and disappeared after intensive antimalarial treatment with quinine. Red pointed cutaneous nodules then appeared and the pains in the bones and joints of the feet became so intense that hospitalization became necessary on May 30th, 1941. The patient appeared as a well-developed but emaciated man with slight anemia, a soft non-transmitted systolic murmur at the apex of the heart and an enlarged hard spleen extending to the level of the umbilicus. Many red nodules in regression were present, especially on the lateral surfaces of the legs. The urine examination was negative and no parasites could be found in the stools. The erythrocytes were 3.3 million per c. mm., 7700 leukocytes (48% granulocytes, 10% monocytes, 42% lymphocytes). No malaria parasites were found. Analgesics were given and the patient remained afebrile during the first week of hospitalization. On June 1st he was seized by a chill followed by fever and profuse sweating; this recurred on the 6th of June and on that day *P. vivax* was demonstrated. After antimalarial treatment, the patient remained afebrile until his discharge on the 30th of June. The red cell count increased to 3.8 million per c. mm. and the size of the spleen was unchanged.

**CASE 2.** B. C., a 34 year old, single, male had experienced several episodes of malaria in the preceding 7 years. In April 1941 he

remained for 2 months in an area where both Carrion's disease and malaria are endemic. On the 20th of June he developed chills followed by fever, which recurred the following morning at the same hour. Despite quinine medication the fever continued, anemia and slight icterus developed and the pain in the bones became quite intense. He also had migratory pains in the joints of the left wrist, elbows and feet and when they were located in the maxilla they were so severe as to make it impossible for him to masticate food. Pain was also present in the left upper quadrant of the abdomen and he was told that he had a "big spleen". In the first week of August, edema of the lower extremities was noticed. On admission on August 20th, 1941, he appeared well developed, undernourished, with marked anemia and pallor of the skin, and a heart normal in size with soft and non-propagated hemic murmurs. The spleen reached the level of the umbilicus in the left mid-clavicular line. A few small lymph nodes, the size of a pea, were noted in the neck, axilla, epitrochlear and inguinal regions. Urine examination was normal. The erythrocyte count was 3.82 million per c. mm.; 8000 leukocytes (56% granulocytes, 1% eosinophils, 18% monocytes and 25% lymphocytes). The fever continued to fluctuate between 37° and 38° C. for nearly a month and then subsided. The pains in the bones and the joints persisted but finally disappeared altogether on the 22nd of October. A few pinpoint verrugae became visible and rapidly increased in size, the anemia improved markedly, the pains faded away and the patient was discharged on the 15th of November, 1941, in very good general condition. Approximately one week after his discharge the chills and fever recurred, the pains in the bones and joints reappeared and a marked involution and disappearance of many of the verrugae was noted. *P. vivax* was found in the smears of the peripheral blood. Quinine was again given with disappearance of the malarial manifestations. The spleen decreased only slightly in size.

It is possible that this patient contracted malaria and Carrion's disease at the same time. The verrugae regressed rapidly after a recurrence of vivax malaria.

**CASE 3.** V. C., a 17 year old Indian farm-worker who had lived all of his life in the high mountains of Peru, in December of 1939 visited an area where Carrion's disease is endemic. Two months later he was suddenly seized with a chill which was followed

by fever. The chills did not recur but the fever was continuous for nearly one month. The patient became pale and anemic with extreme malaise, dyspnea on effort and anorexia; quinine was given without any improvement. He then moved to an area where Carrion's disease does not exist but where malaria is endemic, and here he promptly recovered.

In August, 1940, he noticed several red points in the skin which grew to the size of a pea, representing the eruptive stage of Carrion's disease. In the 2nd week of August chills occurred every day at noon, followed by high fever which lasted only a few hours, profuse sweating, anemia, cough and mucopurulent expectoration. The patient came to the Dos de Mayo hospital in Lima on September 2nd. He appeared to be a well-developed, well-nourished pale young man with profuse sweating and murmurs noted at the apex of the heart and with an enlarged spleen reaching almost to the umbilicus. Verrugae of pinpoint to pea size were distributed irregularly over the skin, but mainly on the lateral surfaces of the legs, most of them in regression. There were also several round hyperpigmented areas, 1 cm. in size, corresponding to the locations of previously implanted verrugae. The urine examination was normal. Blood counts: 2 million erythrocytes per c. mm., 8300 leukocytes, 12.6 gm. hemoglobin, and 28.35 hematocrit. The differential count showed 35% granulocytes (metamyelocytes 2%, stab cells 11% and segmented cells 22%), 3% basophils, 4% monocytes and 58% lymphocytes. *P. vivax* was demonstrated in the blood smears. Under quinine treatment the spleen decreased markedly in size and, on September 21st when the patient was discharged, it could no longer be palpated.

This case illustrates an intense anemia, resistant to quinine treatment, corresponding B.b.a. contracted 2 months earlier while in an area where Carrion's disease is endemic. Later during the eruptive stage of the disease the patient had a vivax malaria.

CASE 4. V. Ch., a 20 year old, single, Indian miner, came from an area where Carrion's disease and malaria are both endemic. In the second week of March, 1938 he developed malaise, loss of appetite, vomiting and a productive cough, with mucopurulent sputum. He entered the hospital on the first of April. Blood counts: (April 3rd) 2.4 million erythrocytes and 6900 white cells per c. mm. (granulocytes 43%, eosinophils 4%, monocytes 12% and lymphocytes 41%); there

were 2 normoblasts per 100 leukocytes. Six weeks later the patient left the hospital markedly improved. In the 2nd week of May he noticed pains in the bones of the extremities especially in the right shoulder. Pin point verrugae in the skin was noticed the first week of June. The patient came to the hospital on the 4th of August to have a verruga of the left lower lid removed surgically. Besides these verrugae, the only abnormal finding was an enlarged spleen reaching 2 fingerbreadths below the left costal margin. The blood counts on admission were as follows: erythrocytes 5.82 million per c. mm., leukocytes 9000. On the 11th of August the patient developed sudden chills. Blood counts: 3.89 million erythrocytes per c. mm., 5900 leukocytes (65% granulocytes [14% stab cells and 51% segmented forms], 4% eosinophils, 1% basophils, 12% monocytes and 18% lymphocytes). Several ring forms of *P. falciparum* were found. The fever and other symptoms disappeared with antimalarial treatment and most of the verrugae regressed quite rapidly.

Carrion's disease and a falciparum malaria were apparently contracted at the same time by this patient. Because of his splenomegaly, profuse sweating and monocytosis, he was given quinine with remission of his fever and anemia. The diagnosis of malaria complicating Carrion's disease was later confirmed.

CASE 5. O. B., a 21 year old Peruvian, spent 4 days in the last week of April, 1941, in an area where Carrion's disease is endemic and then went to work in a place where malaria is endemic. On June 7th, 1941, he noticed malaise and profuse sweating followed by a high and continuous fever. The patient became anemic and was bedridden in the second week of June, continuing with the high fever despite the intensive antimalarial treatment. He developed headaches and on several occasions epistaxis and bilious vomiting along with anorexia, marked polydipsia, sweating with cramps occurring in both feet. Later he became delirious, describing imaginary animals and numerous lights of different colors. The urine became very dark. There were also severe pains in the muscles of the extremities. He was hospitalized in Lima for further treatment on June 2nd, 1941, and appeared pale, undernourished, acutely ill with enlargement of the spleen 2 fingerbreadths below the costal margin. Lymph nodes the size of a pea, semi-hard and non-

tender, were palpated in the cervical, axillary, epitrochlear and inguino-crural regions. The pulse was 110, respirations 36 per minute, blood pressure 115/85. The erythrocyte count was 1.13 million per c. mm., hemoglobin 6 gm., white count 8920, reticulocytes 10.2%, and hematocrit 11.55. A few bartonellae were noted in the smears of the peripheral blood. In the next few days there was

a marked clinical improvement, the temperature oscillated between 37° and 38° C., and the erythrocyte count rose. On July 10th he again developed fever preceded by chills, the erythrocyte count dropped from 2.11 to 1.7 million on July 12th, when a few ring forms of *P. vivax* were found in the blood. After intensive antimalarial treatment with quinine and atebriane the patient recovered.

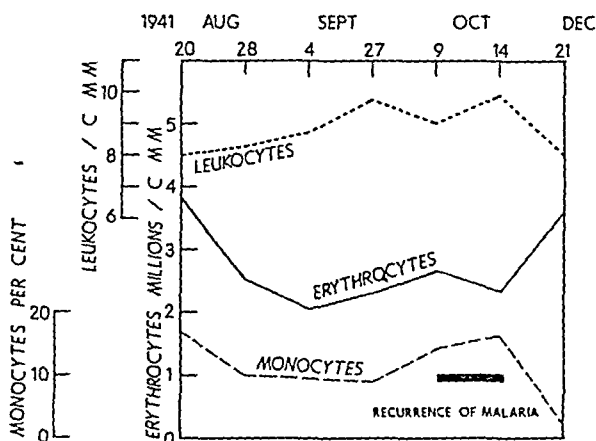


FIG. 1. Patient with erupted verrugae and anemia. The treatment of an intercurrent malaria was followed by decrease in the number of monocytes and a rise in the erythrocyte count.

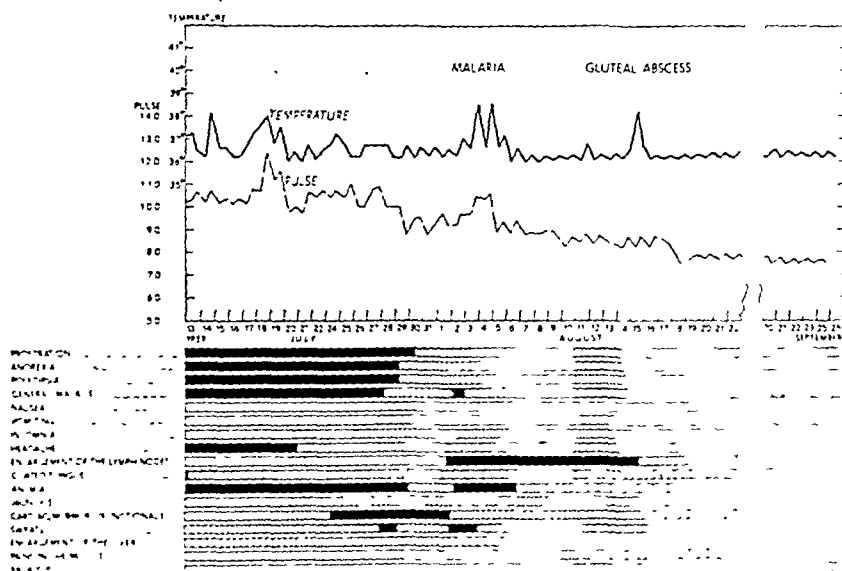


FIG. 2. Recovery phase of *Bartonella bacilliformis* anemia which was followed by a malaria infection. The solid lines represent a marked severity of symptoms; the light line indicates a lesser degree of severity, and the empty blocks represent an absence of symptoms. The greater the distance between lines, the less marked are the symptoms.

This case illustrates an intercurrent malaria infection which occurred shortly after the *B. bacilliformis* had disappeared from the peripheral blood.

CASE 6 (Figs. 2 and 3). R. Ch., a 45 year old, single, Peruvian negro male, worked for 3 years prior to admission, in an area where Carrion's disease is endemic. On June 28th, 1939, he had a chill followed by a fever of 40.3° C. and general malaise. The chill did not recur but the fever continued. On July 4th, 1939, he was admitted to the hospital and physical examination revealed a pale, slight jaundice of the sclerae. A functional systolic murmur was heard at the apex and in the aortic areas of the heart. The liver

developed a ravenous appetite. However, on the 1st of August he complained of headache, vomiting, profuse sweating, recurrent slight jaundice and some fever in the evening. On August 3rd, the erythrocytes numbered 2.07 million per c. mm., leukocytes 9600 (58% granulocytes [3% metamyelocytes, 18% stab cells, 37% segmented forms], 1% basophils, 18% monocytes, 23% lymphocytes). A few of the erythrocytes contained *P. vivax*. The patient was treated with 2.5 gm. of quinine daily given intramuscularly and by mouth, the erythrocyte count decreased to 1.43 million per c. mm. There was a complete remission of symptoms after this medication except for a slight elevation of temperature, on August 14th, which was attributed to local inflammation of the gluteal muscles after injection

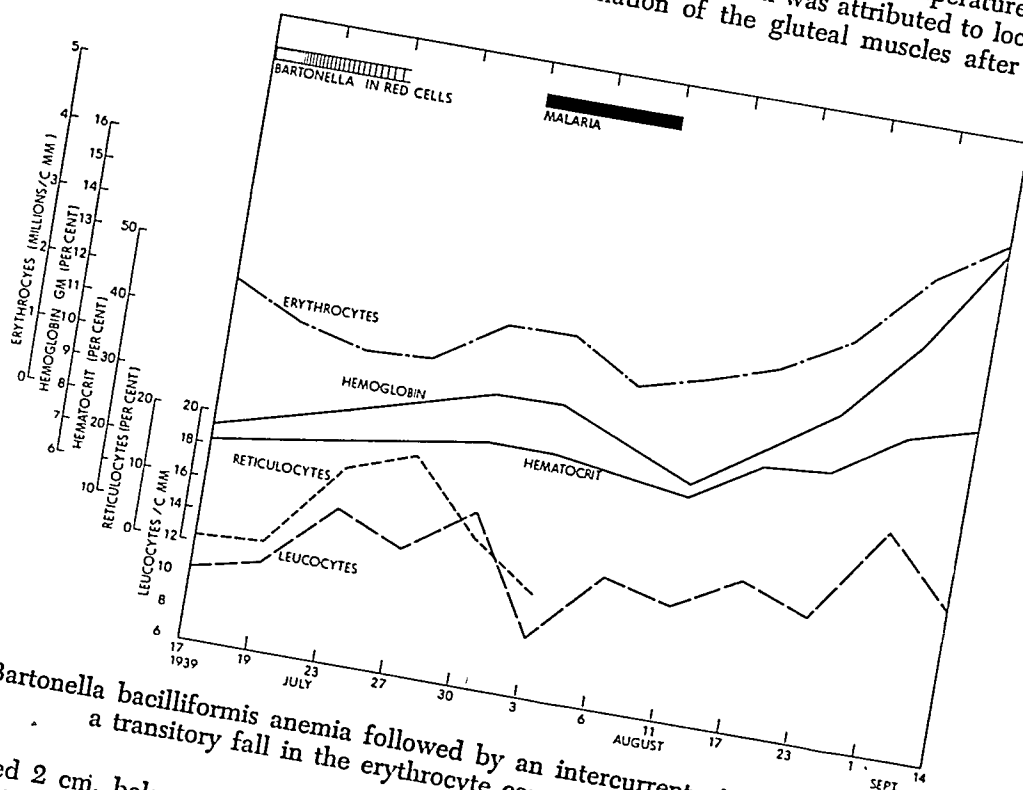


FIG. 3. *Bartonella bacilliformis* anemia followed by an intercurrent vivax malaria producing a transitory fall in the erythrocyte count and hemoglobin.

was palpated 2 cm. below the costal margin in the right midclavicular line. The blood pressure was 120/70, pulse 108 per minute, and the respirations 17. The urine contained traces of albumin and the Wassermann and Kahn tests were negative.

The patient continued to have a slight fever until the 20th of July along with a progressive anemia which on July 23rd recorded 1.28 million red cells per c. mm. with *B. bacilliformis* in the erythrocytes. The bartonellae soon disappeared, the temperature became normal, the anemia improved and the patient

of quinine. The patient left the hospital on September 14th, 1939, with a count of 4.4 million erythrocytes, hemoglobin 15 gm. %, hematocrit 41.42%. The monocytosis disappeared after administration of quinine. Eruption of verrugae had not occurred.

**Discussion.** Intercurrent malaria infection in Carrion's disease is a frequent rather than a rare event as might be gathered from the few isolated reports<sup>2,5,7,9,12</sup>. In previous studies, the author reported such intercurrent infec-



tion in over one-fourth of the hospitalized cases<sup>13,14</sup>. Several features of intercurrent malaria, such as intermittent or remittent fever, profuse sweating, monocytosis and splenomegaly, were originally attributed to Carrion's disease itself. In this series of 22 cases proven to have both diseases, monocytosis was found in every one and splenomegaly in 20. Arce<sup>1</sup> had previously emphasized that splenomegaly does not occur in uncomplicated cases of Carrion's disease.

The immunological course of Carrion's disease seemed little affected by the malaria and in several cases the bartonella disappeared from the red cells as the malaria organisms increased in number. This observation agrees with the findings of Noguchi<sup>10</sup> who experimentally infected monkeys with *B. bacilliformis* and *plasmodia* and found that the development of malaria during convalescence from bartonellosis did not change the course of the

latter. Even the combination of splenectomy and malarial inoculation did not significantly alter the course of the experimental bartonellosis. No fatality occurred in the present series of cases with both diseases.

**Summary.** A study is presented of 22 cases of Carrion's disease with intercurrent malaria. In 3 of these patients who developed malaria following *B. bacilliformis* anemia (Oroya Fever) it was observed that the clinical features were atypical for both diseases. Three cases had malaria in the preeruptive stage and 16 during the eruption of verrugae. The malaria seizures in this last group were typical and easily recognizable, the verrugae rapidly regressed and disappeared. Monocytosis was found in every case of this series and splenomegaly in 20 (91%). The immunological course of Carrion's disease was little affected by the intercurrent malaria.

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# METABOLIC STUDY OF GYNECOMASTIA ASSOCIATED WITH LIVER DISEASE\*

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GYNECOMASTIA is a phenomenon seen in association with many diverse and apparently unrelated diseases. It has generally been ascribed to a derangement of endocrine function involving one or several glands. The study of estrogen metabolism in association with breast enlargement has been the subject of a number of papers, but there is still some controversy as to the quantitative relationship. In addition, the correlation of liver disease and feminizing changes has attracted much interest in recent years, although it was first noted by Corda<sup>4</sup> in 1925.

In the present paper we shall emphasize several of the unusual features of this entire subject. We have studied a case of unilateral gynecomastia with relation to endocrine titers, liver function studies, liver biopsies, effects of administered estrogens, and relation of improvement in liver function to feminizing features, and will attempt to correlate all these findings in the following discussion so that they may serve as a basis for a clearer understanding of the problem and as a means for quantitative studies in other patients. The relation of estrogen metabolism and liver disease to gynecomastia has been repeatedly emphasized because the liver is the principal

organ responsible for estrogen inactivation and conjugation.

**Methods.** The determination of the various endocrine titers was performed by a combination of several previously described methods as modified by Dr. G. R. Kingsley of our biochemical laboratories. The extraction and purification of the urinary estrogen was carried out by the procedure outlined by Salter<sup>20</sup>. The colorimetric determination of the purified estrogen was carried out according to the procedure outlined by Cohen and Bates<sup>3</sup>. The free estrogens were determined by extracting unhydrolyzed urine by the method of Salter. The determination of urinary pregnandiol was accomplished by our modification of the method of Goldzieher<sup>9</sup>. The total 17 keto-steroids were determined by a modification of the methods suggested by Dreckter<sup>5</sup> and Pincus<sup>23</sup>.

Serial liver biopsy studies were made using the intercostal approach with a Vim-Silverman needle. Breast measurements were made with a flexible ruler using a central point stained with indelible dye to insure the same point of measurement each time. Testicular measurements were made with the same flexible ruler.

**Case Summary. History:** A 30 year old Mexican male was admitted to the hospital on August 25th, 1948, with a history of a running nose, headache, a productive cough with thick yellow sputum, fever, and a dull aching in the left chest region for the preceding 3 weeks. For 10 days before entry, he had noted a dull aching pain in the right upper quadrant aggravated by ingestion of food, marked weakness, the appearance of a yellow tint to the skin, golden-colored urine,

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and light-colored stools. He had had considerable nausea with occasional vomiting for several days before entry.

He gave a past history of having ingested 1 to 2 quarts of wine daily for 14 years. During this time, his diet had been very inadequate and he had not eaten at all on the days on which he was drinking heavily. A dietary analysis revealed a deficiency in total calories, all vitamins, and a low protein intake (See Table 1). The patient stated that he had noted a unilateral enlargement of his left breast, a gradual loss of pubic, chest, and axillary hair, a gradual loss of libido, and an inability to conduct intercourse satisfactorily. These symptoms had all appeared during the past 12 to 18 months and had been progressive.

*Physical Examination:* On entry, the patient had a temperature of 99.8°, pulse 96, and respirations 24. He was markedly icteric and appeared chronically ill. The nasal mucous membranes were markedly engorged, but the

chest Roentgen-rays 2 weeks later revealed clearing of the pneumonic area. Liver biopsy shortly after entry revealed portal cirrhosis with conspicuous fatty changes of the liver cells (Fig. 1).

*Course in Hospital:* Following resolution of the pneumonic process with penicillin therapy, a number of basal determinations were made, including liver biopsy, breast size measurements, testicular measurements, complete endocrine studies, and an accurate count of both large and small spider angiomas. The patient then received amniotin (estrone in oil) in a dosage of 40,000 units intramuscularly daily for 1 week, followed by 120,000 units intramuscularly daily for an additional week. At the termination of estrogen administration, during which time the patient had no symptoms, the size of the left breast had increased slightly in diameter, no change in hair growth was noted, a liver biopsy showed improvement, liver function tests showed improvement, and the total

TABLE 1. DAILY DIET ANALYSIS

|               | Prior to Hospital | Regular Diet | Special Liver Therapy Diet |
|---------------|-------------------|--------------|----------------------------|
| Protein       | 127 gm.           | 90 gm.       | 250 gm.                    |
| Carbohydrate  | 55 gm.            | 275 gm.      | 380 gm.                    |
| Fat           | 76 gm.            | 130 gm.      | 65 gm.                     |
| Calories      | 1430              | 2700         | 3100                       |
| Vitamin A     | 1800 I U          | 5000         | 15,000                     |
| Thiamine      | .83 mg.           | 1.5 mg.      | 1.5 mg.                    |
| Riboflavin    | .77 mg.           | 5 mg.        | 1.8                        |
| Ascorbic Acid | 32                | 75           | 200                        |
| Niacin        | 8.8 mg.           | 12           | 16.5                       |

throat was relatively normal. Decreased breath sounds, increased voice sounds, and fine crepitant rales were heard in the right axillary region and in the right lung posteriorly at the base. The abdomen was somewhat distended and shifting dullness was present. The liver edge was palpable 4 finger-breadths below the right costal margin. The spleen was not palpable. The left testicle was markedly atrophic. There was a marked diminution of the axillary, chest, and pubic hair. A diffuse hypertrophy of the left breast region was noted with no abnormality of the nipples. The left breast measured 7 cm. in transverse diameter. Many spider angiomas were seen over the neck, chest, and upper extremities.

*Laboratory Data:* Laboratory studies are summarized in Table 2. The sedimentation rate was 25 mm. per hour. Chest Roentgen-rays revealed a homogeneous density in the apex of the right lower lobe, which was interpreted as representing pneumonia. Follow-up

number of angiomas had decreased. The patient had received no therapy during this time except for the regular hospital diet which was adequate in all constituents.

The patient was next placed on an intensive therapeutic regime consisting of a high protein, high carbohydrate, low fat diet with protein supplements including 1 ounce of nutragest and 1 ounce of protolysate daily. He also received a vitamin B complex intramuscularly daily consisting of 10 mg. thiamine, 10 mg. riboflavin, 5 mg. pyridoxine, 50 mg. calcium pantothenate, and 250 mg. nicotinamide. Crude liver extract (2 cc.) was administered 3 times daily.

The patient showed progressive improvement both by clinical signs and liver function tests (Table 2). The liver size which had been found to be 4 finger-breadths below the right costal margin shortly after entry gradually decreased until no liver edge could be felt at the time of discharge. The elevated icteric index showed a rapid fall. The patient

TABLE 2. LIVER FUNCTION TEST

| Date           | CBC                   | A/G Ratio | Cholesterol Esters | Icterus | Bilirubin<br>(Ind)<br>7.4 (.32)<br>chloroform<br>soluble | Prothrom-<br>bin | Thymol<br>Turbidity | Ceph.<br>Floc. | 2 Hr. Uro-<br>bilinogen       | Galactose<br>Tolerance    | Hippuric<br>Acid (Oral)<br>(Oral) | Brom-<br>sulphalein |
|----------------|-----------------------|-----------|--------------------|---------|--|------------------|---------------------|----------------|-------------------------------|---------------------------|-----------------------------------|---------------------|
| 8/25           | 2.9 50%<br>11,000     | 2.8/4.8   | 175 55%            | 88      |  | 80%              | 17                  | 4              | 1.71 mg.                      | 7 gm./4 hr.<br>urine      | 4.3<br>gm.<br>4 hr.<br>urine      | 35%                 |
| Amniotin begun |                       |           |                    |         |  |                  |                     |                |                               |                           |                                   |                     |
| 9/14           | 3.6 72%<br>9,500      | 3.2/4.9   | 255 59%            | 34      | 2.1 (.05)  |                  | 14                  | 3              | 2.4 mg.                       | 2.5 gm.<br>4 hr.<br>urine | 4.0<br>gm.<br>4 hr.<br>urine      |                     |
| 9/25           | Liver treatment begun |           |                    |         |  |                  |                     |                |                               |                           |                                   |                     |
| 9/28           |                       | 3.8/3.9   | 180 71%            | 15      | 1.7 (.06)  | 75%              |                     |                |                               |                           |                                   | 20%                 |
| 10/6           | 3.5 68%<br>9,000      | 4.3/4.1   | 182 78%            | 10      | 1.0 (.04)  | 70%              | 5.5                 | 2              | .84 mg.<br>1.5 mg.<br>1.0 mg. |                           |                                   |                     |
| 10/15          |                       |           |                    |         |  |                  |                     |                |                               |                           |                                   |                     |
| 10/27          |                       |           | 188 80%            | 7       | .56(.02)   | 75%              | 6                   | 2              |                               |                           |                                   |                     |
| 11/10          | 4.0 80%<br>8,800      | 4.3/3.0   | 182 82%            | 7       | .40(.01)   | 90%              | 2                   | 2              | .8 mg.                        | .20 gm.<br>4 hr.<br>urine | 5.1 gm.<br>4 hr.<br>urine         | 10%                 |

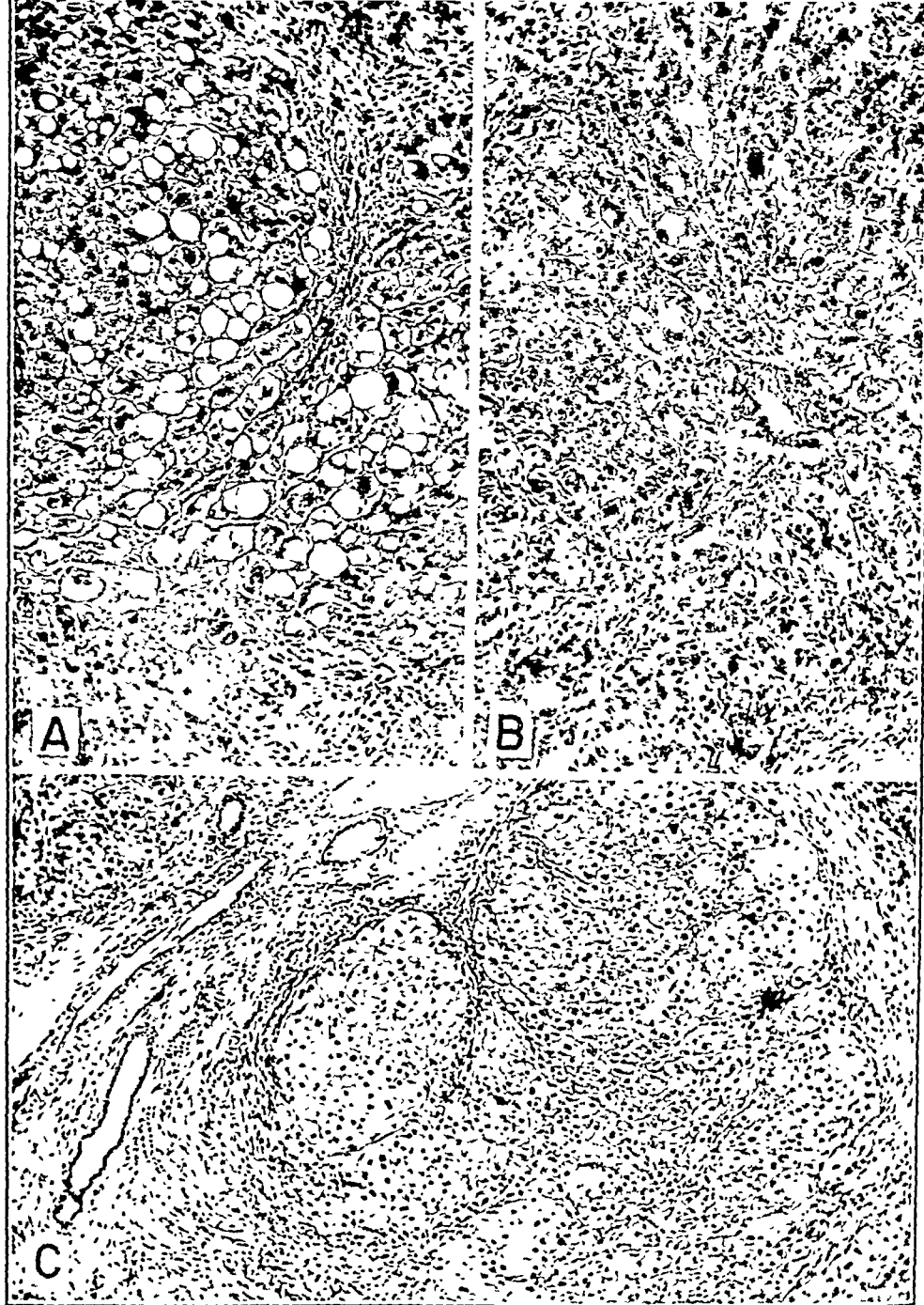


FIG. 1. SERIAL LIVER BIOPSIES

A. Before therapy on August 30, 1918. Marked fatty infiltration. The liver cells show various stages of degeneration. Large quantities of bile pigment are present in canaliculi. Periportal fibrosis is seen with extension of the fibrous septa into the liver lobules.

B. Following estrogen administration on Sept. 30, 1918. Decrease in the degree of fatty infiltration. Fewer degenerating liver cells are seen and the intralobular organization into cords of cells and sinusoids more nearly approaches the normal. Bile pigment is less prominent.

C. After therapy on December 1, 1918. No fatty changes and the liver cells are normal in appearance. An increase in the periportal fibrous tissues with septal extension into the lobule and reduplication of bile ducts is apparent. The lobules are almost completely encircled by fibrous tissue. (Photographs by Wm. L. M. Martinsen, FBPA.)

gained strength, had an increased appetite, and showed a marked decrease in the number of angiomas together with a decrease in the size of the left breast (Table 3). Several weeks after the cessation of estrogen administration, the right breast became swollen and tender. This condition persisted for 2 weeks; then gradually receded.

At the termination of 6 weeks of therapy, the liver biopsy showed marked improvement (Fig. 1), the urinary estrogen excretion had markedly decreased (Table 3), the liver function tests had improved considerably, and the patient was entirely asymptomatic. A marked increase in libido was noted.

*al.*<sup>15</sup> to either a failure of hepatic inactivation of estrogen or a depression of the pituitary gland from malnutrition with a secondary testicular atrophy and decreased androgen excretion. Their quantitative studies revealed a decrease in ketosteroids, but normal estrogen-androgen ratios with a normal follicle-stimulating hormone titer. In the therapy of gynecomastia secondary to malnutrition, no difference in effect was noted whether a regular, high

TABLE 3. ENDOCRINE STUDIES

|               |                 | 8/29/48                            | 9/28/48                           | 11/22/48                          |
|---------------|-----------------|------------------------------------|-----------------------------------|-----------------------------------|
| ANGIOMATA     | Large           | 38                                 |                                   |                                   |
|               | Small           | 35                                 |                                   |                                   |
| BREAST        |                 |                                    | 26                                |                                   |
|               |                 |                                    | 21                                |                                   |
|               | Right           | 2 cm. Horiz.<br>x<br>2 cm. Vert.   | 2 cm. Horiz.<br>x<br>2 cm. Vert.  | 9<br>13                           |
|               | Left            | 6½ cm. Horiz.<br>x<br>6½ cm. Vert. | 9½ cm. Horiz.<br>x<br>9 cm. Vert. | 5½ cm. Horiz.<br>x<br>6 cm. Vert. |
| TESTIS        | Right           |                                    |                                   | 5½ cm. Horiz.<br>x                |
|               | Left (atrophic) | 5 cm. long<br>2.5 cm. long         | 5 cm. long<br>2.5 cm. long        | 3 cm. Vert.                       |
| ESTROGEN      | Total*          | 260 Gamma                          |                                   | 6½ cm. long                       |
|               | Free            | 218 Gamma                          |                                   | 2.5 cm. long                      |
| PREGNANDIAL†  |                 | Normal values                      | 85.5 Gamma                        |                                   |
|               |                 | 3.0 mg./24 hrs.                    | 75 Gamma                          |                                   |
|               |                 | 3.5 mg./24 hrs.                    |                                   | 60 Gamma                          |
| KETOSTEROIDS§ |                 |                                    |                                   | 30 Gamma                          |
|               |                 |                                    |                                   | 6.6 mg./24 hrs.                   |
|               |                 |                                    |                                   | 6.3 mg./24 hrs.                   |

\* Normal (male): 7 to 25 Gamma/24 hrs.  
† Normal (male): less than 3 mg./24 hrs.  
§ Normal (male): 10 to 20 mg./24 hrs.

**Discussion.** Gynecomastia may be secondary to testicular atrophy<sup>2,17</sup>, testicular tumors<sup>6,13</sup>, tumors of the adrenal cortex<sup>27</sup>, hyperthyroidism<sup>28</sup>, pituitary tumors<sup>21</sup>, malnutrition<sup>15</sup>, vitamin deficiency disease<sup>12</sup>, recovery from starvation<sup>25</sup>, and tumors of renal origin<sup>14</sup>. It may also be induced at varying times by the administration of estrogens, androgens, and desoxycortic-

protein, or high vitamin diet was employed.

The association of gynecomastia and testicular atrophy has been known for some time and this has been attributed by some to the fact that the testes inhibit the growth of the breast in males. Testosterone therapy has been employed on this basis but with conflicting results. Testicular atrophy may be secondary to liver disease according to Marrione<sup>20</sup> who found atrophy in a high percentage of cirrhotics, or may be secondary to malnutrition<sup>22</sup>. Klinefelter

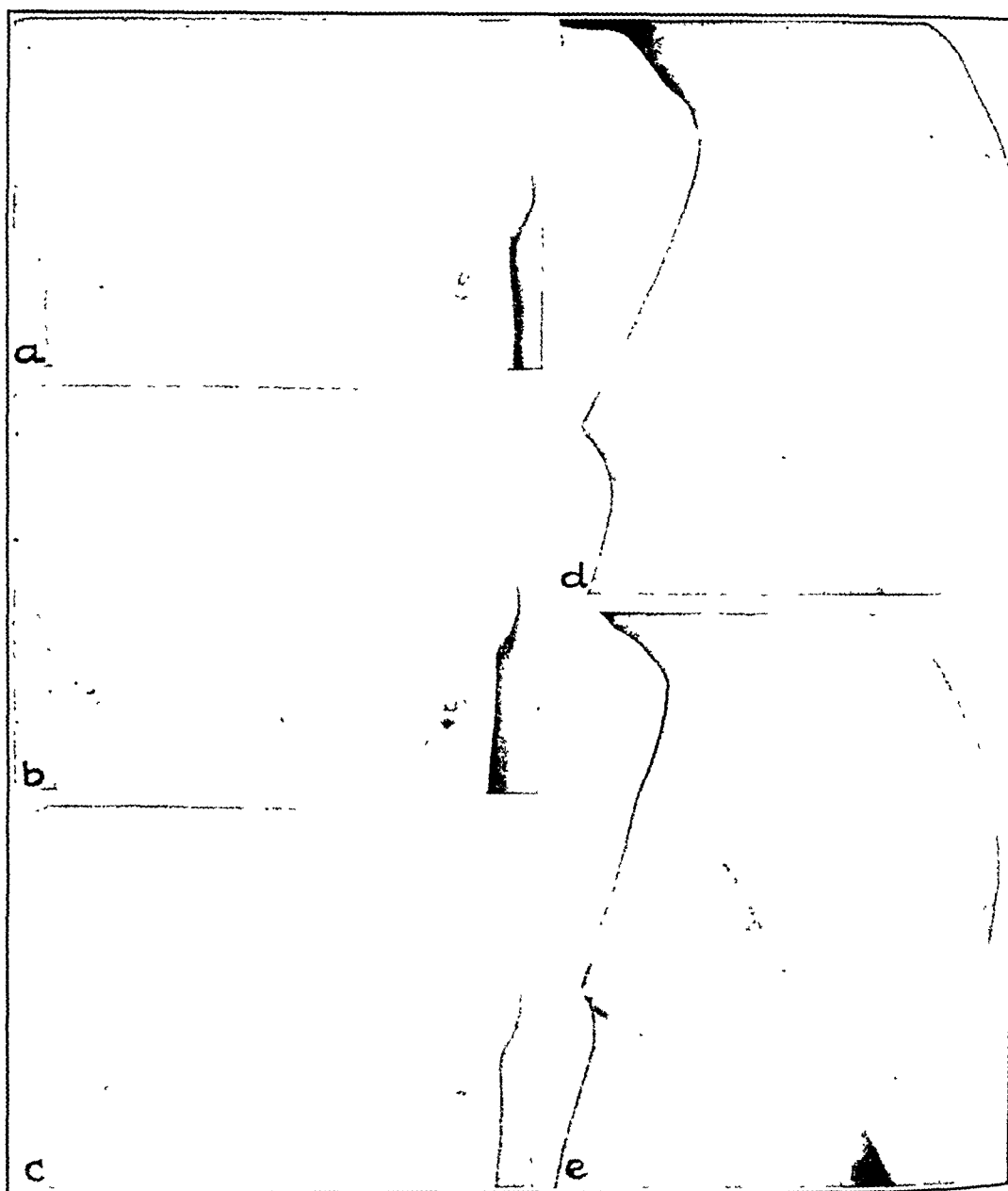


FIG. 2. SERIAL BREAST PHOTOGRAPHS

- A. Anterior view of both breasts before therapy, showing enlargement of left breast.
- B. Anterior view following estrogen administration, showing enlargement of both breasts as compared to (A).
- C. Anterior view showing decrease in size of both breasts (after completion of therapy).
- D. Lateral view of left breast before therapy showing marked enlargement.
- E. Lateral view of left breast after therapy showing decrease in size. (Photographs by Wm L. M. Martinsen, FBPA)

*et al.*<sup>16</sup> have described a syndrome including gynecomastia with atrophic testes showing hyalinization of the seminiferous tubules and postulated that perhaps the inhibiting hormone of the testes on the breast was present in these tubules. Heller and Nelson<sup>11</sup> have described testicular atrophy, azoospermia, and elevation of the gonadotropins frequently associated with enlargement of the breast and loss of hair. They described hyalinization of the seminiferous tubules and clumping of the Leydig cells, and they felt that changes in the Leydig cells might be responsible for the changes in masculine characteristics.

Zondek<sup>30</sup> has stated that the liver is concerned with 95% of estrone inactivation and he has described a test of liver function based on estrogen metabolism. The estrone clearance test is a measure of the ratio of estrone excreted compared to the normal following an intramuscular dose of estrone. He stated that the normal male excreted .5% to 4.5% of the injected estrogen within 48 hours. Patients with hepatitis also excreted a normal percentage unless they were in an advanced state; that is, had lost the function of urea synthesis. Patients with cirrhosis had normal endogenous levels of estrone but excreted an excessive amount following administration. He thought that this test might be useful in determining the prognosis of a given case of liver disease—only in advanced cases with extensive destruction did the liver fail to metabolize estrogens normally.

Glass and associates<sup>7</sup>, having also studied this problem, stated that an increased excretion of estrogens had been noted in cases of gynecomastia associated with testicular tumor, adrenal cortical tumor, or following the administration of estrogens. They thought that gynecomastia associated with malnutrition without liver disease

may represent a deficiency of the same dietary factor necessary for liver inactivation of estrogens. Glass, Edmondson, and Soll<sup>8</sup> studied the effect of administered estradiol and estrone into men with cirrhosis of the liver and found that injected estrogens lose much of their activity in the presence of normal liver function. They stated that the evidence showed that males with advanced liver cirrhosis excrete urinary estrogens in the free form, and they felt that gynecomastia and testicular atrophy were the result of an excess of circulating free (unconjugated) estrogen. Advanced cirrhosis results in the excretion of a large percentage of estrogen particularly in the free form but all their cases of cirrhosis had some increase in total estrogen excretion. Stealy and Stimmel<sup>29</sup> also pointed out that the conjugation of estrogens given to patients with liver disease was markedly impaired. Other workers<sup>10,24</sup> have likewise shown that 90% of injected estradiol could not be recovered in the urine and postulated that the same mechanism of estrogen metabolism holds for both males and females. They showed that the interconversion of estradiol and estrone could take place, both resulting in estriol (the latter reaction was not reversible).

As for the breast enlargement itself most reported cases have shown<sup>18</sup> hyperplasia of ducts and in increase in periductal tissue—the ducts elongate, become tortuous, develop thickened lining (epithel) and show an infiltration of macrophages in the periductile tissues.

*Interpretation of Results:* A number of interesting observations can be made after an analysis of this case. Improvement in the liver status was striking on a regular hospital diet before any supplementary therapy was begun, as evidenced by biopsy, decrease in size, and function tests. The



administration of estrogens was apparently not toxic to the damaged liver since improvement occurred during and after the estrogen administration. In addition, the angiomas count decreased while on estrogens; this also indicated liver improvement.

A correlation between the titer of free and total estrogens and the status of liver function was strikingly illustrated in our study. The fall in estrogen excretion and particularly the decrease in the ratio of free to total estrogens paralleled the improvement in liver functions. This correlation was also demonstrated in that the total estrogen excretion was less after estrogen administrations than without estrogens because of the improvement in liver function during this period.

The changes in breast size were also somewhat correlated with estrogen titers but lagged behind the rate of liver improvement. It is difficult to explain the unilateral gynecomastia except by assuming a different degree of sensitivity to circulating estrogens in the two breasts. In explaining the late enlargement of the right breast following estrogen administration we must again assume a difference in local factors in the two breasts. Klatskin has pointed out that in gynecomastia secondary to malnutrition the breast enlargement may occur not during the period of malnutrition but rather during the recovery phase while on a therapeutic regimen.

The increase in urinary keto-steroids, increase in libido, and increase in the size of the right testicle indicates a close correlation between liver function, adrenal function, and gonadal activity. Lloyd and Williams<sup>19</sup> have pointed out that cirrhosis of the liver is frequently associated with a decrease in lipid content of the adrenals and atrophy of the testes. They also emphasized that the 17-ketosteroid excretion of

male patients with cirrhosis is lower than can be explained on the basis of absent gonadal steroids excretion alone — this suggests that adrenal hormone production is less than normal. This may be the result of high estrogen titers in the blood since this is known to inhibit adrenal function. Lloyd and Williams have postulated that the decrease in the inactive oxidative products of estrogen, which occurs when a diseased liver is unable to inactivate estrogens and form these oxidative products, leads to a decrease in formation of adrenotrophin from the pituitary. This in turn leads to decreased adrenal function with loss of axillary hair and a decrease in the urinary 17-ketosteroids.

The decrease in the total number of spider angiomas during estrogen administration is in contradistinction to the findings of Bean<sup>1</sup> who was able to produce "spiders" by the administration of estrogen, and may have been due to the rapid improvement in liver function.

**Summary.** 1. A review of the relationship between cirrhosis, gynecomastia, and endocrine changes has been given.

2. A detailed metabolic study of a case of cirrhosis with unilateral gynecomastia and other feminizing features has been presented. A careful study of endocrine titers by a modification of previously described methods has been carried out.

3. The correlation between the condition of the liver, the presence of breast changes, and the degree of estrogen inactivation and total excretion has been demonstrated.

4. A striking response in liver function to an ordinary diet, together with a lack of toxic effect on the liver by the administration of estrogens, was noted.

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# LIVER FUNCTION IN DIABETES MELLITUS\*

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DIABETES mellitus in man is still a syndrome of unknown etiology. The major laboratory indications of the disease, hyperglycemia and glycosuria, may occur in a great variety of experimental conditions and disease states. Hyperglycemia and glycosuria can occur with thyrotoxicosis, Cushing's syndrome, liver disease, pituitary lesions and adrenocorticotrophic hormone administration<sup>1</sup>.

In most instances the hyperglycemia can be alleviated by the administration of insulin. This would suggest that an insulin deficiency, either relative or absolute, is the common denominator; but the diabetic state which ensues after total pancreatectomy in man is mild and readily controlled by 25 to 40 units of insulin per day<sup>12</sup>. From an experimental standpoint Soskin has data which point to the liver rather than the pancreas as the major organ in carbohydrate metabolism. Soskin<sup>10</sup> found that the hepatectomized dog had a decreased glucose tolerance, whereas the pancreatectomized animal with a constant insulin infusion had a relatively normal glucose tolerance.

There have been many attempts to incriminate the liver as a factor in the etiology of clinical diabetes, and most of the studies have revealed some impairment in various of the liver function tests. Gray *et al.*<sup>3</sup>, using the colloidal gold test, found a positive test

in 37% of 241 patients. Moreover, they observed the highest incidence of positive tests in the more severe diabetics, particularly those with a history of diabetic acidosis. Meyer, in 1931<sup>7</sup>, concluded that hepatic dysfunction was a frequent occurrence in diabetes mellitus, but the tests used are now recognized as inferior, and many of his patients had complicating biliary tract disease. Rabinowitch<sup>8</sup>, who examined 3000 cases from a diabetic clinic, found hyperbilirubinemia in 27.4% when 0.2 mg. per 100 cc. of bilirubin in the blood was taken as the upper limit of normal. Furthermore, he found that a similar percentage of patients had an elevated urine urobilinogen. His upper limit of normal for bilirubin would now be recognized as low, but there is no ready explanation for the elevated urine urobilinogen. Possibly some of these patients had hepatitis, for it is now realized that homologous serum hepatitis is not uncommon in clinics where frequent venipunctures are done.

It should be appreciated that even present day liver function tests are relatively crude and that minor deviations from the normal in any one test should not be interpreted as a manifestation of liver disease. Also, little reliance should be placed upon certain non-specific tests such as the colloidal gold and cephalin flocculation, as these tests are difficult to run in a routine

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clinical laboratory, and slightly positive tests are even more difficult to interpret.

In this study 8 of the commonly accepted liver function tests have been carried out on a series of 25 diabetics in whom there was clinically no other etiological factor for liver disease. In 15 of the patients the studies were made within 48 hours of their admission to the hospital in severe diabetic acidosis. In 3 cases a liver biopsy was done to detect any changes in the histology of the liver. The tests employed were the

there is little if any derangement of liver function in diabetes as measured by the usual liver function tests. In the 15 patients who entered the hospital in acidosis, in whom one might expect a maximum derangement of carbohydrate metabolism, and by that token perhaps of liver function, the liver functions were strikingly normal. In only 1 patient of the acidosis group was there any significant bromsulfalein retention, and this was only 8%, which is very close to the upper limits of normal.

TABLE 1.—RESULTS OF LIVER FUNCTION TESTS IN 25 DIABETICS

| Patient   | Duration of Diabetes | Age & Sex | Previous Insulin Dose Day REG--PZI | BSP % retention at 45 min. | Serum Bil. mg. per 100 cc 1 min. 30 min. | Prothr. Cont. % | Thymol Turb. | Ceph. Flocc. | Serum Prot. Alb. Glob. gm.% gm.% | Urine Urobil. Ehrlich U. | Icterus Index |     |    |
|-----------|----------------------|-----------|------------------------------------|----------------------------|--|-----------------|--------------|--------------|----------------------------------|--------------------------|---------------|-----|----|
| 1. P.D.   | 15 yrs.              | 30 M      | 40                                 | 40                         | 0  | 0               | .2           | 98           | .88 (5)                          | 0                        | 3.8           | 2.5 |    |
| 2. M.F.   | 8 yrs.               | 37 F      |                                    | 50                         | 0  |                 |              | 100          |                                  | 1+                       |               |     | 5  |
| 3. E.G.   | 4 yrs.               | 32 F      |                                    | 35                         | 0  |                 |              | 85           |                                  | 0                        |               |     | 5  |
| 4. N.H.   | 10 yrs.              | 47 F      | 20                                 | 10                         | 0  | 0               | .02          | 72           | .77                              | 1+                       |               |     |    |
| 5. J.M.   | 1½ yrs.              | 18 M      |                                    | 20                         | 0  | 0               | .02          | 100          | .3                               | 0                        |               |     |    |
| 6. P.M.   | 1½ yrs.              | 23 F      |                                    | 12                         | 0  |                 |              | 75           | .52                              | 0                        |               |     | 6  |
| 7. W.S.   | 19 yrs.              | 55 M      | 10                                 | 40                         | 8  | 0.2             | 0.4          | .63          |                                  |                          |               |     | .8 |
| 8. J.P.   | 6 yrs.               | 28 M      |                                    | 60                         | 0  | 0.2             | 0.2          | .72          |                                  |                          | 4.1           | 3.1 | .4 |
| 9. C.D.A. | 15 yrs.              | 42 F      | 45                                 | 40                         | 4  |                 |              | 75           |                                  | 0                        |               |     | .6 |
| 10. S.G.  | 6 yrs.               | 22 M      |                                    | 60                         | 0  | .16             | .58          | 100          | .54                              | 1+                       |               |     | .6 |
| 11. E.M.  | 4 yrs.               | 35 F      | 30                                 | 30                         | 0  |                 |              | 68           |                                  | 1                        |               |     | .4 |
| 12. J.I.  | 4 yrs.               | 25 M      |                                    | 40                         | 2  |                 |              | 86           |                                  | 0                        |               |     | .6 |
| 13. T.D.  | 5 wks.               | 33 M      | 0                                  | 0                          | 0  | .1              | .4           | 90           | .64                              | 0                        |               |     | .5 |
| 14. M.K.  | 15 yrs.              | 42 F      |                                    | 40                         | 0  | .2              | .4           | 90           | .7                               | 1+                       | 4.0           | 2.1 | .2 |
| 15. F.M.  | 12 yrs.              | 38 F      |                                    | 35                         | 0  | .15             | .6           | 75           | .68                              | 1+                       | 3.9           | 2.0 | .5 |

THE ABOVE TESTS WERE DONE WITHIN 24 TO 48 HOURS OF ENTRY TO THE HOSPITAL IN SEVERE ACIDOSIS\*\*

|            |         |      |    |    |    |     |     |     |     |     |     |     |      |     |
|------------|---------|------|----|----|----|-----|-----|-----|-----|-----|-----|-----|------|-----|
| 16. C.L.   | 6 yrs.  | 55 M |    | 60 | 1  |     |     | 100 | 3.  | (6) | 5.4 | 1.8 | .6   | 5 * |
| 17. P.E.L. | 9 yrs.  | 52 M |    |    | 2  | 0.8 | 1.4 | 80  | 2.5 |     | 5.6 | 2.0 | 0.8  |     |
| 18. H.H.   | 1st Dg. | 56 M | 20 |    | 8  | 0.4 | 1.2 | 50  | 4.  |     | 6.2 | 1.6 |      | 5   |
| 19. C.V.T. | 3 mos.  | 60 M |    |    | 1  |     |     | 75  | 2   |     | 4.4 | 2.6 |      | 5   |
| 20. N.B.   | 7 yrs.  | 55 M |    |    | 4  | 0.2 | 1.0 | 100 | 5.  |     |     |     |      |     |
| 21. J.N.   | 1 yr.   | 35 M | 20 | 60 | 0  | 0.2 | 0.8 | 92  | 5.  |     | 5.2 | 3.6 |      | *   |
| 22. J.A.   | 1 yr.   | 61 M |    | 45 | 0  | 0.1 | 0.4 | 50  | 2.5 |     | 4.6 | 2.8 | 1.2  |     |
| 23. A.W.   | 12 yrs. | 51 M |    | 70 | 15 | 0.2 | 0.4 | 100 | 4.  |     | 4.0 | 3.0 | 0.48 |     |
| 24. H.H.   | 6 mos.  | 50 M |    |    | 5  | 0.4 | 1.2 | 75  | 5.  |     | 4.8 | 1.1 |      |     |
| 25. J.H.   | 3 yrs.  | 55 M | 10 |    | 2  | 0.3 | 0.7 | 85  | 1.  |     | 4.2 | 2.8 |      |     |

\* Biopsy with normal liver.

\*\* All of the patients in acidosis had a CO<sub>2</sub> combining power of less than 20 volumes %.

bromsulfalein retention at 45 minutes, using 5 mg. per Kg., the thymol turbidity<sup>5,6</sup>, the cephalin flocculation<sup>4</sup>, the van den Bergh 1 minute and 30 minutes<sup>2</sup>, the prothrombin content<sup>11</sup>, the urine urobilinogen<sup>12</sup>, the icterus index and the serum proteins. It was not possible in every patient to do all the tests mentioned, but in every case sufficient tests were done to give a spectrum of liver function.

Results. Although this series is small, the results (see Table 1) indicate that

Another case showed 15% retention, but this patient had some congestive failure. In no case of the series was there a complete battery of tests indicating hepatic disease.

In 3 of the patients whose livers were somewhat enlarged on physical examination, the histological sections on punch biopsy were perfectly normal. Even special strains for glycogen and fat revealed no abnormality.

It is appreciated that the function of the liver concerned with carbohydrate

metabolism may not be measured by any of the tests employed and that some new test may reveal an abnormality of liver function. The galactose tolerance test which is a good test of liver function, might be expected to be abnormal in the diabetic with his deranged carbohydrate metabolism, but the results were found to be no different in a series of 10 normals and 10 diabetics reported by Roe and Schwartzman<sup>9</sup>.

This study furnishes no evidence that hepatic disease is associated with dia-

betes mellitus. This is in agreement with Wilder<sup>14</sup> who found evidence of hepatic disease in only 0.7% of 2584 cases of diabetes mellitus, and only rarely did there seem to be any causal relation between the 2 diseases.

**Summary.** A battery of the usual liver function tests has been employed in the study of a series of 25 diabetics, in 15 of whom there had been a recent episode of acidosis. No evidence was obtained to indicate that impaired liver function is associated with clinical diabetes mellitus.

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# THE INFLUENCE OF PHYSICAL THERAPY PROCEDURES ON THE INTRA-ARTICULAR TEMPERATURE OF NORMAL AND ARTHRITIC SUBJECTS\*

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ALTHOUGH physical therapy has long been regarded as one of the therapeutic agents of proven value in arthritis, we know of no studies to determine changes in the temperature of the diseased joint following the use of these various procedures. Knowledge of the best way to produce these changes is obviously of immediate and considerable practical value. Lonergan<sup>3</sup> found a 1° F. rise in the temperature of a dog joint on the application of long wave diathermy for a period of 1 hour. Continuous application of this agent resulting in the death of the animal from shock produced a rise of 7° F. in the left hip joint. Lonergan also reported one experiment in which long wave diathermy was applied to the human knee joint. A thermocouple was placed in the popliteal space with the knee acutely flexed on it. After a 70 minute treatment, a temperature rise of slightly more than 4° F. was observed. Several other reports<sup>2,4</sup> have appeared on the joint temperature of dogs following heating. One group of investigators<sup>2</sup> has calculated cooling curves, and estimated relative rates of circulation through the joint tissue. Horvath and Hollander<sup>1</sup> have determined the temperatures of knee and

elbow joints in both normal subjects and patients suffering from joint diseases. An excellent correlation between the joint temperature and the clinical activity in patients suffering from rheumatoid arthritis was observed.

**Methods.** The procedures employed to modify the joint temperature will be given at appropriate places in the text. Only a single agent was employed on a patient at any one time. The skin and deep temperatures were measured by methods previously described<sup>1</sup>. The subjects were supine and the thermocouple was in place within the joint for at least 20 to 30 minutes prior to the control observations. In the majority of the tests environmental temperature was  $24^{\circ} \pm 2^{\circ}$  C.; in the remaining it was 18° C.

**Results.** Passive motion of the joint through its pain-free range is a common therapeutic procedure. The data presented in Table 1 were obtained prior to, and following, such movement in 8 subjects. Although skin temperature over the joint was not influenced by this procedure, a mean elevation of 0.8° F. occurred within the joint. However, considerable variation in response was observed. In Subject 6, only the first few movements were accomplished without pain, and, since the range was definitely limited, it was impossible to move the joint to any great extent. The

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TABLE 1. THE INFLUENCE OF PASSIVE MOVEMENT\* OF THE KNEE JOINT ON THE TEMPERATURE WITHIN THE JOINT

| Patient                 | Initial Temperature °F. | Maximum Change °F. |
|-------------------------|-------------------------|--------------------|
| 1. Normal               | 90.6                    | 0.5                |
| 2. Normal               | 88.6                    | 2.1                |
| 3. Rh. Arthritis        | 96.0                    | 2.0                |
|                         | 96.6                    | 0.1                |
| 4. Rh. Arthritis        | 90.8                    | 1.4                |
| 5. Rh. Arthritis        | 92.8                    | -0.2               |
| 6. Rh. Arthritis        | 92.3                    | -0.9**             |
| 7. Degen. Joint Disease | 93.9                    | 1.4                |
| 8. Gout                 | 96.1                    | 0.8                |
| Mean Change             |                         | 0.8                |

\* 10 to 15 movements without pain.

\*\* Painful.

the sixth subject the elbow was treated and the maximum elevation in this joint was 3.6° F. while the skin temperature rose 1.6° F. A significantly greater rise ( $t = 1.88$ ) in the joint than in the surface temperature was observed. The mean difference between the 2 positions was 1.6° F. This variation was more apparent when higher energy inputs were being employed. A typical cooling curve following this type of heat therapy is shown in Figure 1. The sharp initial drop and succeeding retarded rate of cooling was observed in all patients.

Table 3 contains the data obtained

TABLE 2. EFFECT OF MICROWAVE\* ENERGY (12.2 cm.) ON THE TEMPERATURE OF THE KNEE JOINT

| Patient           | Initial Temperature °F. |       | Maximum Increase °F. |       |
|-------------------|-------------------------|-------|----------------------|-------|
|                   | Surface                 | Joint | Surface              | Joint |
| 9. Reiter's Syn.  | 86.0                    | 90.6  | 6.0                  | 5.7   |
| Reiter's Syn.     | 87.5                    | 89.4  | 6.4                  | 8.4   |
| 10. Rh. Arthritis | 91.9                    | 92.9  | 5.0                  | 8.2   |
| 11. Rh. Arthritis | 84.5                    | 88.1  | 6.3                  | 6.9   |
| 13. Rh. Arthritis | 88.9                    | 92.9  | 7.6                  | 3.6   |
| 14. Rh. Arthritis | 93.7                    | 94.8  | 2.4                  | 2.5   |
| Rh. Arthritis     | 94.0                    | 96.0  | 1.1                  | 1.1   |

\* All applications were for a period of 15 minutes. Patients 9 to 12 were given 50 watts; patients 13 to 14 were given 35 watts.

degree and intensity of movement probably modify the rise in temperature. Active weight bearing movements were also performed in 2 normal subjects and a mean rise of 2.3° F. was observed. More information on this aspect will be presented when the amount of work performed by the patient's joint can be accurately evaluated.

Heating of the joint and adjacent tissues by the application of high frequency electrical energy was studied in a number of subjects. A micro wave generator (wave length 12.2 cm.), employing a director 4 inches in diameter, placed at a distance of 2 inches from the joint was used. The duration of the heating period was exactly 15 minutes. The data obtained in 5 patients are presented in Table 2. In

following the application of conventional short wave diathermy. The inductive method with 3 turns of the coil around the joint was employed. The heating period was 20 minutes. The maximum elevation of the joint temperature was approximately to a level of 101° F. The initial joint temperature apparently exerted no influence upon this final value. Note especially the changes in Subject 15, a normal individual, and in Subject 18, an individual suffering from degenerative joint disease. The elevation of both joint and surface temperatures was approximately equivalent, the mean surface temperature being some 0.6° F. higher than the mean joint temperature. In Figure 2 are shown typical cooling curves obtained on a normal individual and on an individual suffering from

rheumatoid arthritis. The differences between the two cooling curves are mainly those relating to the duration and rate of cooling of the joint following therapy. The relative rates of cooling were quite different in different disease entities. Calculations of  $K$ , the cooling constant, on 4 types of individuals are presented below. In the

normal subject  $K$  was  $-1.14$ ; in quiescent rheumatoid arthritis,  $-0.90$ ; active rheumatoid arthritis,  $-0.56$ ; and for degenerative joint disease,  $-0.35$ .

The application of an infra-red baker to the knee and surrounding areas for a period of 20 minutes resulted in rather large increases in surface temperature with minimal elevations of the

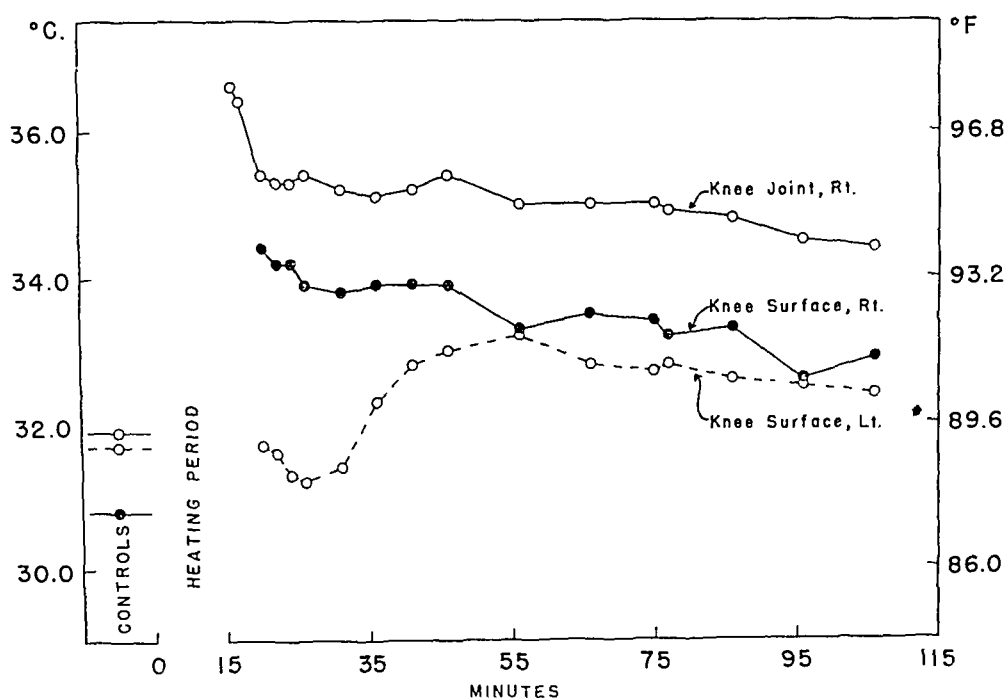


FIG. 1. The joint and surface temperatures in a patient with Reiter's disease before and after the application of micro wave energy with a 4 inch circular director and a power output of 50 watts.

TABLE 3. ELEVATION OF THE TEMPERATURE OF THE KNEE JOINTS AND SURFACES FOLLOWING VARIOUS THERAPEUTIC PROCEDURES

| Patient                  | Mode and Duration of Treatment    | Initial Temperature °F. |       | Maximum Temperature °F. |       |
|--------------------------|-----------------------------------|-------------------------|-------|-------------------------|-------|
|                          |                                   | Surface                 | Joint | Surface                 | Joint |
| 15. Normal               |                                   | 85.2                    | 90.8  | 9.6                     | 10.2  |
| 16. Rh. Arthritis        | Short Wave Diathermy (20 minutes) | 84.7                    | 86.0  | 12.9                    | 9.8   |
| 17. Rh. Arthritis        |                                   | 91.8                    | 96.6  | 3.6                     | 4.6   |
| 18. Degen. Joint Disease |                                   | 92.8                    | 96.4  | 5.4                     | 4.8   |
| 9. Reiter's Syndrome     |                                   | 89.8                    | 93.3  | 6.7                     | 5.7   |
| 19. Gout                 |                                   | —                       | 96.0  | —                       | 3.7   |
| 20. Rh. Arthritis        | Infra Red Baker (30 minutes)      | 91.0                    | 92.8  | 8.2                     | 1.7   |
| 21. Degen. Joint Disease |                                   | 92.1                    | 90.6  | 5.9                     | 4.4   |
| 22. Rh. Arthritis        | Luminous Lamp (20 minutes)        | 94.8                    | 97.3  | 5.7                     | 1.0   |
| 23. Rh. Arthritis        | Paraffin Pack                     | 96.1                    | 97.0  | 6.6                     | 0.8   |
| 24. Rh. Arthritis        | (26 minutes)                      | 89.9                    | 95.2  | 15.6                    | 3.1   |

° Paraffin temperature 148°F.

°° Paraffin temperature 130°F.



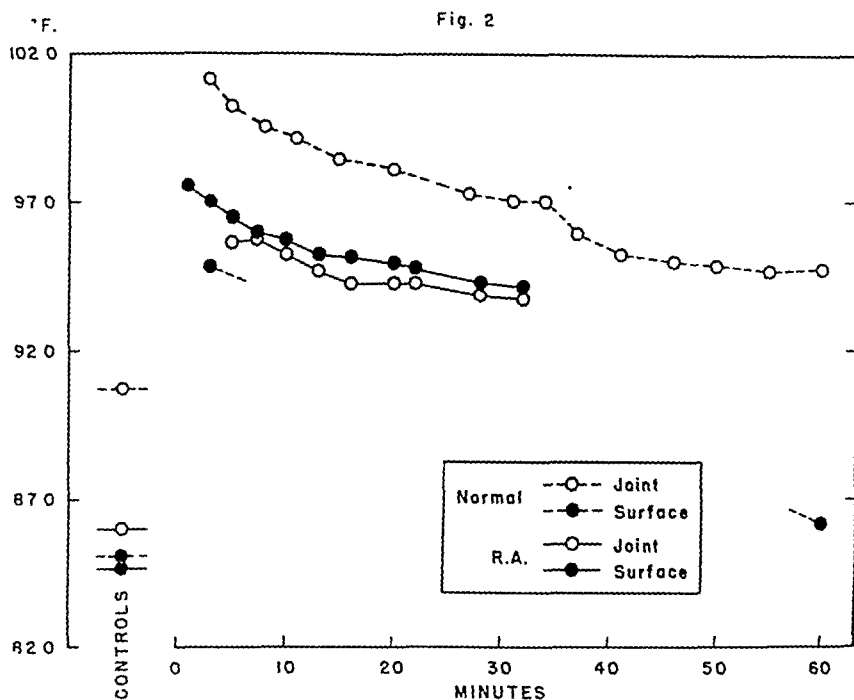


FIG. 2. The joint and surface temperatures in a patient with quiescent rheumatoid arthritis and a normal subject before and after local heating for 20 minutes employing short wave diathermy (induction coil method).

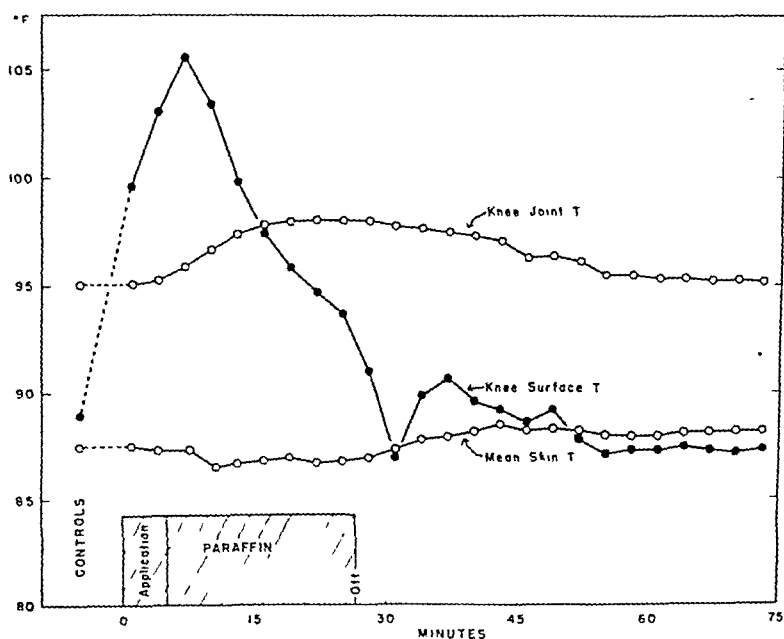


FIG. 3. The joint temperature in a patient with rheumatoid arthritis before, during, and after application of paraffin.

deep or joint temperature. The mean maximum change in joint temperature was  $+3.3^{\circ}$  F. When an infra-red lamp was applied for a period of 20 minutes a small change,  $1^{\circ}$  F., occurred in the deep temperature, whereas the surface temperature rose approximately  $6^{\circ}$  F. at the completion of the treatment.

The effectiveness of the application of paraffin over a joint depends to a great extent upon the temperature at which the paraffin is being applied. In one experiment in which the temperature of the paraffin was  $130^{\circ}$  F. a mean elevation of the joint temperature to  $3.1^{\circ}$  F. was observed. In Figure 3 is shown the maintained response of the joint temperature to this therapeutic procedure. If, however, the paraffin was too hot, namely at a temperature of  $148^{\circ}$  F., there was little elevation in the joint temperature. The discrepancy between these procedures probably lies in the fact that the thickness of the layers is definitely related to the temperature of the paraffin being applied.

Several experiments were performed in which individuals were subjected to hydrotherapeutic procedures. Treatment in the Hubbard Tank with the water temperature  $101^{\circ}$  F. resulted in an increase in joint temperature of  $0.7^{\circ}$  F. It should be noted that the rectal temperature during this period of immersion had also risen  $0.6^{\circ}$  F. This effect was relatively transitory and disappeared within 20 to 30 minutes. In additional experiments it was attempted to determine the influence of reflex vaso-dilation on the joint temperature in the extremity being reflexly vaso-dilated. The knee joint temperature of the leg that was immersed up to the knee failed to rise as a consequence of the treatment. This was interesting, in view of the fact that conduction heat was apparently of no great importance in raising the joint temperature. The ankle joint on the contralateral limb had its temperature

measured during the same interval and failed to exhibit any change during and following treatment. On the other hand it should be noted that there was a definite reflex vaso-dilation as evidenced by the rise in the toe temperature of the contralateral side. The toe temperature was elevated  $9^{\circ}$  F. to a final temperature of  $94.6^{\circ}$  F. It is significant that reflex vaso-dilation of the skin vessels was not accompanied by a similar reflex vaso-dilation in the deep vessels.

**Discussion.** Classification of heating procedures by their effect on joint temperature is now possible. This method of determining temperatures may also prove to be a means of measuring the efficiency of circulation in the synovial membrane. The various procedures employed to elevate the intra-articular temperature do so in a manner dependent apparently upon their relative ability to penetrate to the deeper tissues. This is most evident in comparison of the results of infra-red irradiation, where a mean rise in temperature of slightly over  $3^{\circ}$  F. was observed, with values of  $6^{\circ}$  to  $8^{\circ}$  F. elevation of temperature following the application of convective types of heating. It is also interesting to note that the duration of the cooling curve appears to be primarily a reflection of the intensity of the elevation of the joint temperature.

The significance of the various types of cooling curves observed in individuals suffering from joint disease is not at the moment apparent. It is interesting, however, that the cooling curve is more prolonged in those individuals suffering from degenerative joint disease. A probable explanation of this observation lies in 2 factors: 1, the excessive amount of fibrous tissue in the thickened synovial membrane and increased adipose tissue around the joint which interferes with ready loss of heat from the part; 2, definite changes in circulation within the diseased joint. It

is extremely suggestive that the cooling curve of normal individuals is so much more rapid than that of those suffering from arthritic involvements.

It has not yet been shown that raising the joint temperature, in treating various forms of arthritis, is necessarily beneficial. It is well known that in many cases of active arthritis those forms of physical therapy that raise the temperature most, namely short wave diathermy and micro wave, clinically appear to aggravate pain in the joints. On the other hand forms of therapy like infra-red which have minor effects on the joints and exert their primary effects on the surface appear to be of much greater value. It is apparent from these results that re-evaluation of the procedures of physical therapy chosen for treatment in arthritic disorders should be made with the reaction of the joint tissues in mind and should not be dependent purely upon surface changes. This is of greater interest since it has been shown<sup>1</sup> that the changes in joint circulation do not necessarily parallel those of the skin but frequently are even opposed, which indicates at least a reflex reciprocal flow of blood between the integument and deeper tissues.

**Conclusions.** It has been possible to evaluate the results of various methods of applying physical therapy by simultaneous determination of internal joint temperature and surface temperature.

Passive motion of a joint increased joint temperature to a slight degree. A more marked effect was observed following active weight bearing motions.

Passive heating of joints was accomplished by means of short wave diathermy, a micro wave generator, an infra red baker, application of paraffin or immersion in hot water. All these methods of applying heat increased the skin temperature as anticipated.

Following hydrotherapy, however, the joint temperature was only slightly elevated.

More marked heating of the joint was obtained from radiant heat and the application of paraffin to the surface.

The greatest elevation of joint temperature occurred following application of high frequency electrical energy, *i.e.*, short wave diathermy or micro wave. The relative rate of cooling of joints after passive heating was more rapid in normal than in rheumatoid arthritic or osteoarthritic joints.

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# THE METABOLISM OF THIOCYANATE AFTER PROLONGED ADMINISTRATION IN MAN\*

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INVESTIGATIONS of the distribution of thiocyanate ion in measuring the extracellular fluid volume has resulted in a better understanding of its metabolism during short sojourns within the body<sup>1,5,6,13</sup>. Whereas almost all thiocyanate can be recovered in the urine after a single dose<sup>13</sup>, discrepancies between the daily intake and urinary output have been demonstrated after repeated administration of the drug for prolonged periods<sup>1,6,11,12</sup>. In explanation of this, routes of excretion other than the kidneys in man<sup>12</sup>, and intra-cellular storage in dogs<sup>1,6</sup> have been suggested, but never conclusively demonstrated. Since thiocyanates are still used in the treatment of essential hypertension and in the estimation of extracellular fluid volume it seemed of importance to determine the fate of this drug after long continued use in man.

**Materials.** Fifteen cases, 9 normotensive and 6 hypertensive, were selected for study because they had little evidence of impaired renal function or abnormal hydration. They were divided into 3 groups:

GROUP 1 consisted of 2 normal subjects (the authors) both of whom received single

doses of 1500 mg. of sodium thiocyanate§ intravenously. Then, after an interval of 4 weeks, Subject E.D.F. received a single oral dose of 1260 mg. of potassium thiocyanate†. GROUP 2 consisted of 9 cases hospitalized 7 to 13 days for conditions other than acute illness. Eight received oral potassium thiocyanate in doses to 200 to 400 mg. per day, while 1 received daily doses of 400 mg. of sodium thiocyanate intravenously. In both groups 24-hour, as well as other appropriate collections of urine were made throughout the period of study. GROUP 3 consisted of 5 cases studied as out-patients at 7 to 14 day intervals for 4 to 15 weeks. Four were selected because of their cooperation and reliability in obtaining 24 hour collections of urine and taking prescribed doses of oral potassium thiocyanate (120 to 360 mg. per day) depending upon the individual case. To avoid criticism of data obtained in this manner, one of us, F.C.M. followed a similar regimen for 4 weeks collecting all urine voided throughout the entire period until no further thiocyanate appeared therein.

**Methods.** Determinations of the serum concentration of thiocyanate were made by the method of Crandall and Anderson<sup>5</sup>, modified<sup>6</sup>, and adapted to the Coleman junior spectrophotometer<sup>17</sup>. The "natural thiocyanate color" of the serum<sup>3</sup>, which remained constant in any given case from day to day, was determined prior to administration of the drug. From this value (range 0.7 to 1.2 mg. per 100 cc.) correction was made in each instance to obtain the actual serum con-

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\*\* On leave from the Mary Hitchcock Memorial Hospital, and Dartmouth Medical School, Hanover, New Hampshire.

§ Sodium thiocyanate in sterile saline containing 50 mg. per cc. used exclusively throughout this study for intravenous administration.

† Potassium thiocyanate "Enseals"—Eli Lilly Co., Indianapolis, Indiana, was used exclusively throughout this study for oral administration.

centration of thiocyanate. Urinary thiocyanate determinations were made by pipetting 2 cc. of urine with 10 cc. of 10% trichloroacetic acid and filtering after gentle agitation. Three cc. of the filtrate were then pipetted into each of 2 colorimeter tubes. To one, 3 cc. of ferric nitrate reagent<sup>6</sup> was added and to the other, which served as a blank, 3 cc. of distilled water. Readings were made within 5 minutes with the Coleman junior spectrophotometer at a wave length of 480 millimicrons. A thiocyanate-like color developed by ferric nitrate found in the urine<sup>6</sup> of all subjects while receiving no thiocyanate was determined prior to administration of the drug and correlated with the specific gravity. A factor was thus determined for every 0.001 of specific gravity in each subject and corrections made to determine the actual amount of thiocyanate in each 24 hour collection. The stool specimens were first thoroughly mixed in a Waring blender with known volumes of water and filtered prior to determination of thiocyanate concentration. Blanks were utilized in the same manner as described for the urine, and, because no natural color appeared in the feces, further correction was unnecessary. The thiocyanate content of the sweat (induced by heat) was determined in the same manner as the plasma.

As applied in this study, the term "thiocyanate space" reflects the total fluid volume in which thiocyanate is distributed including the plasma volume and that amount known to enter certain cells<sup>5,13</sup>. Since the fluid volume in this space remains constant under normal conditions of hydration<sup>13,14</sup>, repeated doses of thiocyanate should increase the concentration in this fluid volume proportionately, unless after prolonged administration, (1) thiocyanate enters cells to a greater degree, (2) is excreted by routes other than the kidneys, or (3) is destroyed. Because the serum thiocyanate is in relative equilibrium with all components of the "thiocyanate space," the serum increment each day should be equivalent to the increment within the entire "thiocyanate space" throughout any period during administration of the drug. Thus, it should be possible to determine the amount in mg. retained at any moment by multiplying the plasma concentration of thiocyanate in mg. per cc. by the "thiocyanate space" in cc. Furthermore, the per cent daily increment retained within the fluid volume of the "thiocyanate space" as calculated above plus the per cent excreted in the 24 hour urine, feces, and sweat, should approach all of the daily intake, unless, as previously suggested, undue cellular deposition or destruction occurred.

**Results. GROUP 1.** The subjects of this group were each given a single dose of thiocyanate in an attempt to determine whether all of the drug could be recovered in the urine following acute administration (Table 1). Subject E.D.F., who received 1500 mg. of sodium thiocyanate intravenously excreted a total of 1460 mg., (97%) of the original amount in the urine throughout a period of 14 days. After that time no further thiocyanate could be recovered in the serum or urine. Similarly, Subject F.C.M., who received the same amount of drug intravenously, excreted a total of 836 mg. of thiocyanate during the first 5 days when the experiment was terminated. Multiplying the serum concentration (0.043 mg. per cc.) by the thiocyanate space (15,200 cc.) it was calculated that 654 mg. of the drug remained within the fluid volume of the "thiocyanate space" after 5 days. Therefore, a total of 1490 mg. (836 + 654 mg.), or 98.7%, of the dose could be accounted for at that time (Table 1). At another time, subject E.D.F. received 1260 mg. of oral potassium thiocyanate as a single dose. Following administration of the drug all urine voided was collected until thiocyanate failed to appear therein. After 13 days, 1212 mg. of the original 1260 mg. (96%) of drug administered was recovered. Obviously, therefore, almost all thiocyanate was accounted for by urinary excretion after single doses of the drug whether administered by the intravenous or oral route.

It is of interest that whereas in dogs receiving intravenous thiocyanate a marked increase of the apparent volume of distribution occurred with time<sup>6</sup>, the apparent volume of distribution after single intravenous doses in both subjects of Group 1 of the present experiments in man increased only slightly throughout the first 48 to 72 hours, thereafter returning towards

TABLE 1.—ACUTE ADMINISTRATION OF THIOCYANATE PER CENT OF DRUG RECOVERED AFTER SINGLE DOSE

| Subject | Route and Amount<br>Thiocyanate Given<br>Mg. | Time From<br>Administration<br>Days | Thiocyanate<br>Space<br>cc. | Serum<br>Conc.<br>Mg. % | Amount of<br>SCN to be<br>Accounted for<br>Mg. | Total<br>Urinary<br>Output<br>Mg. | Total<br>Urinary<br>Recovery of<br>SCN Per Cent |
|---------|--|-------------------------------------|-----------------------------|-------------------------|--|-----------------------------------|---|
| E.D.F.  | 1500 I.V.                                    | 14                                  | 15,300                      | 0                       | 1500   | 1460                              | 97.3  |
| F.C.M.  | 1500 I.V.                                    | 5                                   | 15,200                      | 4.3                     | 846  | 836                               | 98.7  |
| E.D.F.  | 1260 Oral                                    | 13                                  | 15,300                      | 0                       | 1260   | 1212                              | 96.2  |

TABLE 2.—THE APPARENT VOLUME OF DISTRIBUTION OF SODIUM THIOCYANATE DURING 5 DAYS AFTER SINGLE INTRAVENOUS INJECTION

| Subject | Age | Sex | Weight<br>Kgm. | Time<br>After<br>Injection<br>Hours | Dose<br>Intravenous<br>Mg. | Sodium Thiocyanate              |                        |                           |                                     |                  |
|---------|-----|-----|----------------|-------------------------------------|----------------------------|---------------------------------|------------------------|---------------------------|-------------------------------------|------------------|
|         |     |     |                |                                     |                            | Serum<br>Concentration<br>Mg. % | Output<br>Urine<br>Mg. | Amount<br>Retained<br>Mg. | Volume of<br>Distribution<br>Liters | % Body<br>Weight |
| F.C.M.  | 35  | M   | 71             | 2                                   | 1500                       | 9.8                             | 13                     | 1487                      | 15.2                                | 21.4             |
|         |     |     |                | 4                                   |                            | 9.3                             | 26                     | 1461                      | 15.7                                | 22.1             |
|         |     |     |                | 6                                   |                            | 9.1                             | 35                     | 1426                      | 15.7                                | 22.1             |
|         |     |     |                | 24                                  |                            | 7.1                             | 230                    | 1196                      | 16.9                                | 23.8             |
|         |     |     |                | 48                                  |                            | 6.4                             | 244                    | 952                       | 14.9                                | 21.0             |
|         |     |     |                | 72                                  |                            | 5.7                             | 110                    | 842                       | 14.8                                | 20.9             |
|         |     |     |                | 96                                  |                            | 4.9                             | 99                     | 743                       | 15.2                                | 21.2             |
| E.D.F.  | 36  | M   | 73             | 5                                   | 1500                       | 4.3                             | 70                     | 673                       | 15.6                                | 22.5             |
|         |     |     |                | 7                                   |                            | 9.7                             | 23                     | 1477                      | 15.3                                | 21.0             |
|         |     |     |                | 24                                  |                            | 9.3                             | 22                     | 1455                      | 15.7                                | 21.5             |
|         |     |     |                | 48                                  |                            | 9.0                             | 14                     | 1441                      | 16.0                                | 21.9             |
|         |     |     |                | 72                                  |                            | 7.2                             | 233                    | 1208                      | 16.8                                | 23.0             |
|         |     |     |                | 96                                  |                            | 5.5                             | 237                    | 971                       | 17.6                                | 24.1             |
|         |     |     |                | 120                                 |                            | 4.6                             | 194                    | 777                       | 16.9                                | 23.1             |
|         |     |     |                |                                     |                            | 3.2                             | 115                    | 511                       | 16.0                                | 21.9             |

the values obtained at the end of 2 hours which averaged 21.2% of the body weight (Table 2). Although these values are higher than those obtained with inulin<sup>10</sup>, they correspond to those of other workers<sup>10,13</sup> for the apparent volume of distribution of thiocyanate in man.

GROUP 2. In all of these cases receiving continued daily doses of the drug the serum concentrations of thiocyanate increased rapidly throughout the first 4 to 5 days, and then remained relatively constant. (Fig. 1). However, once a serum concentration became established there were wide fluctuations in the total urinary output of thiocyanate from day to day (Fig. 1). That these fluctuations were not due to

the dose or serum concentration of the drug was evidenced by the fact that in 2 cases (W.W. and L. W-H.) similar fluctuations were observed not only at the serum levels established after receiving 200 mg. of thiocyanate for 6 days, but also at higher serum levels established after the dose had been increased to 400 mg. per day for several days. Furthermore, in all cases the sum of the per cent retained in the "thiocyanate space" and the per cent excreted in the urine approached 100% of the daily intake only during the first 2 to 3 days. Thereafter, an average of 74% (range -78 to +195% of the daily intake could be accounted for (Fig. 1).

In 3 cases 24 hour stool collections

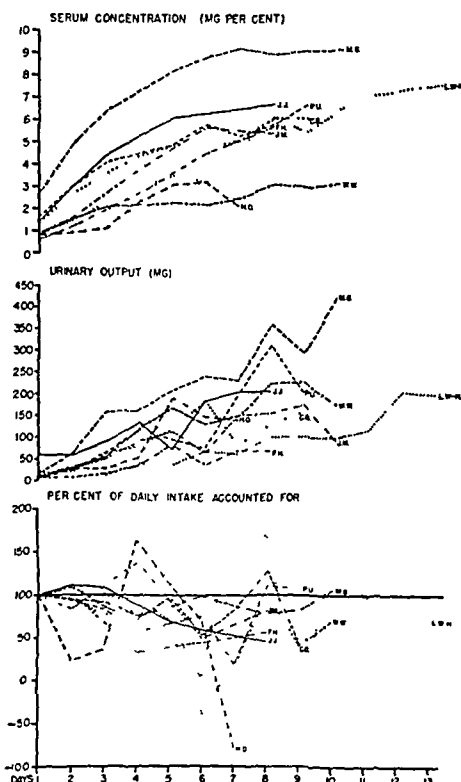


FIG. 1. Serum concentration, urinary excretion and per cent of daily intake of thiocyanate accounted for in the subjects of Group 2. The urinary output fluctuates widely after the first 4 to 5 days and after the first 2 to 3 days less than 100% of the daily intake is accounted for in the majority of instances. Subjects L. W-H. and W. W. received 200 mg. of oral potassium thiocyanate a day for 6 days, then 400 mg. for the remainder of the period of study.

made on 3 to 6 different days at different serum concentrations revealed an average daily thiocyanate excretion in the feces of 3.7 mg. (range 1 to 20 mg.) which represented a negligible portion of the intake. Moreover, in 1 case (F.C.M.) with a serum concentration of 4.9 mg. per 100 cc. the concentration in the sweat (heat induced) was only 0.8 mg. %.

GROUP 3. All cases received oral potassium thiocyanate for 2 to 15 weeks in amounts sufficient to maintain blood levels from 4 to 14 mg. per 100 cc. for periods of 2 to 8 weeks.

obtained when a single dose was given, ranged from 20 to 36% less than the amount calculated to have remained in the fluid volume of the "thiocyanate space" at the time of withdrawal (Table 3).

In order to confirm the above results, one of us, F.C.M., ingested 4440 mg. of potassium thiocyanate in divided doses of 360 mg. per day for a period of 13.3 days. All urine was collected throughout this period and continued after the drug was withdrawn until the serum and urine were completely cleared of thiocyanate. The

TABLE 3.—PROLONGED ADMINISTRATION OF THIOCYANATE PER CENT OF DRUG UNACCOUNTED FOR AFTER WITHDRAWAL

*At Time of Withdrawal of KSCN*

| <i>Subject</i> | <i>Duration of Administration Weeks</i> | <i>Serum Concentration Mg. %</i> | <i>Calculated Amount KSCN Present in "Thiocyanate Space" Mg.</i> |
|----------------|---|----------------------------------|--|
| K. M.          | 11                                      | 4.5                              | 665  |
| G. B.          | 15                                      | 13.8                             | 1900   |
| M. S.          | 9                                       | 7.1                              | 792  |
| D. M.          | 4                                       | 5.8                              | 1190   |

*After Withdrawal of KSCN*

| <i>Subject</i> | <i>Time After Withdrawal Days</i> | <i>Serum Concentration Mg. %</i> | <i>Total Urinary Output of KSCN Mg.</i> | <i>% KSCN Unaccounted For</i> |
|----------------|-----------------------------------|----------------------------------|---|-------------------------------|
| K. M.          | 12                                | 0                                | 483                                     | 20                            |
| G. B.          | 28                                | 0                                | 1212                                    | 36                            |
| M. S.          | 10                                | 1.6                              | 637                                     | 20                            |
| D. M.          | 23                                | 0                                | 939                                     | 22                            |

Throughout the period when blood levels were relatively constant, weekly determinations of the 24 hour urinary output in all cases revealed discrepancies between the daily intake and the total urinary output similar to those noted in Group 2.

In 4 cases after varying periods of daily administration thiocyanate was discontinued and all urine collected, either to the point of complete disappearance of thiocyanate from both the serum and urine, or to a point of known serum concentration. In these cases the amount of thiocyanate recovered in the urine, in contrast to the results

average values of 3.7 mg. per day for loss in the feces and 8 mg. per day (0.008 mg. per cc. x 1000 cc.) for loss through imperceptible sweat<sup>15</sup> were used to calculate the total loss via these routes. Calculated thus, the fecal and imperceptible sweat loss was 269 mg. throughout the 23 day period, while the urinary recovery was 2670 mg. The total recovery of 2939 mg. (2670 mg. + 269 mg.) of the administered 4440 mg. left a deficit of 34% of the thiocyanate administered. In contrast, after acute administration in the same subject there was a deficit



of only 1.3% exclusive of possible excretion via the sweat or feces.

**Discussion.** The results of these studies indicated that temporary cellular storage occurred after the acute administration of thiocyanate since the "apparent volume of distribution" increased during the first 48 to 72 hours. However, such storage was only transient and almost all of the drug was recovered in the urine.

In contrast, during prolonged administration there were marked discrepancies between the daily intake and urinary output, confirming the observations of previous authors<sup>1,6,11,12</sup>. Such discrepancies apparently occurred coincident to the establishment of a relatively stable serum concentration regardless of the daily dose or of the route of administration. That routes of excretion other than the kidneys did not explain such discrepancies during prolonged dosage was indicated by the fact that negligible amounts of the daily intake were recovered in the stool and sweat despite relatively high serum concentrations.

Since thiocyanate was not excreted in the feces or sweat to any significant degree, the failure to account for all of the drug administered after prolonged use suggested that it had either entered cells or had been altered within the body. If intracellular storage had occurred the subjects who had received thiocyanate for long periods (Group 3) would have accumulated considerable amounts during the 2 to 15 weeks of administration. After such cellular accumulation withdrawal of the drug should have been followed by an even greater urinary recovery of thiocyanate than had been calculated to remain within the "thiocyanate space." However, upon withdrawal of the drug after prolonged administration no evidence of such intracellular accumulation was apparent in the urinary recoveries. In fact, the total urinary excre-

tion was even less than that calculated to have been in the "thiocyanate space" at the time the drug was discontinued. This indirect evidence was confirmed by the results of Subject F.C.M. In this instance, whereas after the acute administration of a single dose only 1.3% of the total amount given was not recovered, after prolonged administration 34% of the amount ingested was lost. Since excretion by routes other than the kidneys and intracellular storage failed to explain such great losses of thiocyanate it was concluded that permanent alteration of the ion must have occurred within the body after prolonged dosage.

The recent studies of Wood and Williams<sup>16</sup> using radioactive thiocyanate demonstrated destruction of minute amounts of the ion in the thyroid of rats after 24 hours. It is possible in view of the present investigation that greater amounts of the thiocyanate ion would have been destroyed after long continued administration. Although the product formed in the thyroid gland has not been determined, these same authors had previously demonstrated that in rats minute amounts of thiocyanate may be converted into sulfate<sup>19</sup>. Furthermore, Estes and Keith<sup>7</sup> recently reported elevation of the serum sulfate in a few patients who had received thiocyanate for long periods of time. Although suggestive, these studies do not prove that thiocyanate is catabolized to sulfate in man; nor do they exclude the possibility that thiocyanate is utilized to form other sulfur containing products within the body.

It is impossible to determine from the present data whether the clinical effects of thiocyanate in hypertensive patients are associated with this apparent mechanism for destroying thiocyanate after prolonged administration. That such a relationship may exist, however, is suggested by the

observations that the thiocyanate ion does not exhibit hypotensive properties upon acute administration in doses sufficient to obtain therapeutic blood levels<sup>9</sup>, while clinical responses to the drug, when they occur, frequently are not observed until after several weeks of continued administration<sup>2,4</sup>.

**Summary and Conclusions.** 1. After a single dose of thiocyanate nearly all of the drug can be accounted for on the basis of urinary excretion.

2. By contrast, after prolonged administration either orally or intravenously, discrepancies occur between

the total amount excreted and the amount retained, suggesting that under these circumstances the drug is either stored intracellularly or destroyed *in vivo*.

3. Following withdrawal of the drug after a period of prolonged dosage the total amount recovered in the urine is far less than that calculated to be present at the time medication was discontinued, indicating that during prolonged administration destruction rather than storage of thiocyanate ion occurs.

4. Negligible amounts of thiocyanate are excreted in the feces or the sweat.

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# DIAZOMETHANE POISONING: REPORT OF A FATAL CASE WITH AUTOPSY

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THE present report is concerned with what is believed to be the first instance of fatal diazomethane poisoning in man. Diazomethane was discovered by Pechmann<sup>9</sup> in 1894. A search of all reference sources available since that year, including all issues of the Quarterly Cumulative Index Medicus and its predecessors, the Index Catalogue of the Library of the Surgeon-General's Office of the United States Army, and various texts and monographs on toxicology, chemistry and industrial medicine too numerous to mention, reveals but a single published clinical case of diazomethane poisoning. This was reported by Sunderman, Connor and Fields<sup>10</sup> in 1938. The lack of emphasis on the extreme toxicity of this agent in the chemical literature, which was noted by these authors, apparently persists at the present writing.

Pechmann<sup>9</sup> described diazomethane as being extremely poisonous. Various ill effects experienced by those working with the gas were subsequently noted briefly. These included denudation of the skin and mucous membranes<sup>5</sup>; irritation of the skin and rendering of the fingers so tender that it was difficult to pick up a pin<sup>8</sup>; chest pains, fever and severe asthmatic symptoms<sup>2</sup>; development of a supersensitivity "so that it is almost impossible to work even carefully with diazomethane without being subjected to attacks of asthma and fever"<sup>1</sup>. Arndt described it as "an especially insidious poison"<sup>1</sup>. While these warnings, included in a technical journal, would seem to be adequate, a

full realization of the serious character of the toxic effects produced by diazomethane apparently does not exist.

Diazomethane is a very unstable, odorless, yellowish gas which is of great usefulness chemically as a methylating agent. Because of its high degree of chemical activity it not only presents a toxic hazard but is explosive as well. For this reason it is generally not employed in its gaseous form, but is dissolved in ether or benzene in which it is readily soluble. Some details of its nature and uses may be found in the article by Sunderman *et al.*<sup>10</sup>.

CASE REPORT. H.W., a 28 year old, white male chemist, working in a research institute, was engaged in an investigation of ergothioneine, a procedure which involved the employment of various chemical agents, including phosphorus pentachloride, hydrogen chloride, acetyl chloride and diazomethane. On November 25, 1948, he worked with these substances in a trial run of a preliminary step in his project. On December 2 he repeated the process on a much larger scale. Reluctant to leave a distillation operation which was in progress, he ate his lunch in the laboratory. It consisted of a rather greasy hamburger sandwich, which might have some significance because of the fat solubility of diazomethane. The patient inadvertently inhaled the gases produced in the course of his experiment, although he was working under a laboratory hood. During his activities he became aware of a tickling discomfort in the throat, and began to cough. The cough was short, hacking, dry and persistent. On December 3 he worked in the laboratory as usual, but went home early because of fatigue, substernal soreness and the cough which had continued without cessation from its onset. That night he called his physician to whom he mentioned the nature of his research and the recent exposure to chemical irritants. At that

time physical examination was negative. The oral temperature was 102.4° F. He was given 300,000 units of procaine penicillin G in aqueous suspension intramuscularly. The following day, December 4, he took several doses of aspirin because of a severe headache, and seemed improved. When re-examined by his physician in the early evening he revealed a few fine crepitant rales at the base of the left lung; the oral temperature was 100.2° F. In general his condition seemed considerably better. He was given a second dose of penicillin. However, during the night he became quite dyspneic and his cough was even more harassing than before. At 3 a.m. on December 5, after a brief episode of chilliness, his temperature rose to 104° F. At 7 a.m. his physician found signs of what he believed to be pneumonitis at the base of the left lung.

I first saw the patient at noon on December 5. The history revealed the fact that he had inhaled the chemicals mentioned above. The irritating nature of phosphorus pentachloride, hydrogen chloride and acetyl chloride was fully appreciated. However, the patient offered no information as to the character of diazomethane, of which neither his physician nor I had any knowledge. At this examination there was rapid, gasping respiration, harassing short cough and some degree of apprehension. There was also marked flaring of the alae nasae and retraction of the intercostal, supra-sternal and supraclavicular spaces on inspiration. Signs suggestive of pneumonitis involving the left lung were again present. These consisted of slight to moderate impairment of the percussion note, bronchovesicular breath sounds and numerous fine and coarse crepitant rales. A few fine crepitant rales were also present below the right clavicle. The temperature was still 104° F., the cardiac rate 90 and the respiratory rate 30 per minute. The blood pressure was 128/80. At 1:35 p.m. the patient was admitted to Jewish Hospital.

At 4 p.m. it was found that dullness was present throughout the right upper lobe and much of the middle lobe. In the same areas there were also bronchial breath sounds, coarse and fine crepitant rales but little change in vocal resonance. The patient complained of being unable to fill his lungs with air. Moderate cyanosis was present in spite of oxygen therapy. It was increasingly evident that we were dealing with no ordinary pneumonic process. Although a second consultant who examined the patient was of the opinion that this was a fulminating pneumonia, probably pneumococcal complicating an earlier virus pneumonitis, attempts to discover the possible role of diazomethane as the cause of a chemical pneumonia were continued. However, the

day being Sunday, few sources of information could be reached and none of these could clarify the question. It was not until the morning of December 6 that we learned that diazomethane was in all probability the cause of the patient's symptoms.

There was little change in the pulmonary signs from the evening of December 5 until the patient died at 4:45 p.m. on December 6, about 100 hours after definite exposure to diazomethane. However, the cardiovascular manifestations were of considerable interest. The blood pressure at 1:35 p.m. on December 5 was 134/80 and the cardiac rate was 100 per minute. At 4:30 p.m. the blood pressure was 146/80 and the cardiac rate 136 per minute. At 8:30 p.m. the readings were 170/88 and 140 respectively; at 1 a.m. on December 6, 180/90 and 136; at 7 a.m. 170/90 and 176, from which point on the blood pressure dropped slowly throughout the day while the cardiac rate maintained a level in excess of 170 per minute until death occurred. From 1 a.m. on December 6 the respiratory rate averaged 44 per minute. Except for one instance, following sponging, the temperature never fell below 104°, rising to 106° terminally. All measures to control the progressive shock, anoxia and hyperpyrexia were of no avail. It is worthy of note that frank pulmonary edema was never evident by physical signs.

Other manifestations which occurred included mental confusion which first appeared late in the evening of December 5; muscular twitchings which seemed to respond to 5% intravenous dextrose infusion; coma which developed quite suddenly at 8 a.m. on December 6; vomiting of a small amount of brownish material, strongly positive for occult blood, at noon on December 6, and the vomiting of about 750 cc. of partly coagulated blood terminally.

Treatment consisted of oxygen therapy; sedation for the cough, restlessness and sub-sternal distress by means of small subcutaneous doses of morphine sulphate; ice caps and alcohol sponges for the hyperthermia; penicillin, combined sulfadiazine and sulfamerizine, and dehydrostreptomycin. Intravenous or hypodermic dextrose in normal saline solution or in distilled water, in 5% concentration, were given as the state of the patient's fluid balance seemed to indicate. Blood plasma, whole blood transfusion and adrenal cortex extract were employed to combat the state of shock.

The laboratory studies were largely limited by the patient's critical status and brief illness. A blood count on December 5 revealed 14.5 gm. of hemoglobin with 4.5 million erythrocytes. The leukocytes numbered 11,300

of which 83% were neutrophils, 6% were monocytes and 11% lymphocytes. Of each 100 neutrophils 54% were filamentous forms and 46% were nonfilamentous. On December 6 there was a marked leukocytosis, over and above obvious hemoconcentration. While the red blood cell count was 5.6 million, with a hemoglobin reading of 15.5 grams, the leukocytes were 23,600 in number, the differential count being approximately that of the preceding day. The urine was typical of a patient suffering from a very acute febrile reaction, the specific gravity being 1.035, with 4 plus albumin, 1 plus acetone and 0.5% of sugar (apparently due to therapy) present. There

two main bronchi and all of the bronchial branches showed a deep red, swollen velvety surface, covered in many places by a thin layer of catsup-colored exudate.

The *myocardium* was pale, brown, soft and cloudy. The *liver* weighed 1550 gm. and appeared somewhat small for the size and age of the patient. There was marked mottling of the surface, in many irregular areas having a pale yellow color in contrast to more congested dark brown segments. Section revealed lobules with pale yellow centers surrounded by red rings. There was a greasy aspect to the cut surface.

The *esophagus* showed a swollen, dark red



FIG. 1. Section through Wall of Trachea ( $\times 100$ ).

FIG. 2. Section of Lung and Bronchiole ( $\times 100$ ).

were also some hyaline and occasional granular casts. The blood sugar, after therapy was begun in the hospital, was 366 mg. and the urea nitrogen was 17 per 100 cc. of blood. A single blood culture showed no growth.

**AUTOPSY** (by Dr. Benjamin Gouley, chief coroner's physician, 19 hours after death) The salient gross features were in the respiratory system. Both *lungs* were large and bulky; the right weighing 850 gm. and the left 800 gm. On section they revealed deep, red moist parenchyma studded with numerous tubercle-like gray points. Many of these under pressure were seen to be semi-liquid, exuding small points of pus. There were no gross consolidations in either lung. The *trachea*, the

in places almost black mucosa, particularly in the lower half where there were surface erosions and necrosis of surface epithelium. The *stomach* was moderately dilated, its mucosa somewhat congested, but showed nothing of the striking change seen in the esophagus. The congestion was most marked at the cardia, fading rapidly toward the fundus. It contained 300 cc. of dark, almost black fluid. The *duodenum* likewise showed mucosal congestion but no ulceration.

The *thymus* was enlarged and cellular for the patient's age level. While fatty tissue was present, there were numerous islands of grayish-red and red thymic tissue throughout.

The *brain* revealed on section a rather

striking spotting of red throughout the white matter, seen almost equally in all lobes of the cerebrum. The cortex showed nothing of note.

HISTOLOGIC EXAMINATION of the *trachea* and main stem *bronchi* showed the ciliated

epithelium to be almost entirely lost and the mucosa markedly thickened by edema and congestion. There was enormous engorgement of capillaries and small veins. The tissue forming the background of the mucosal structure

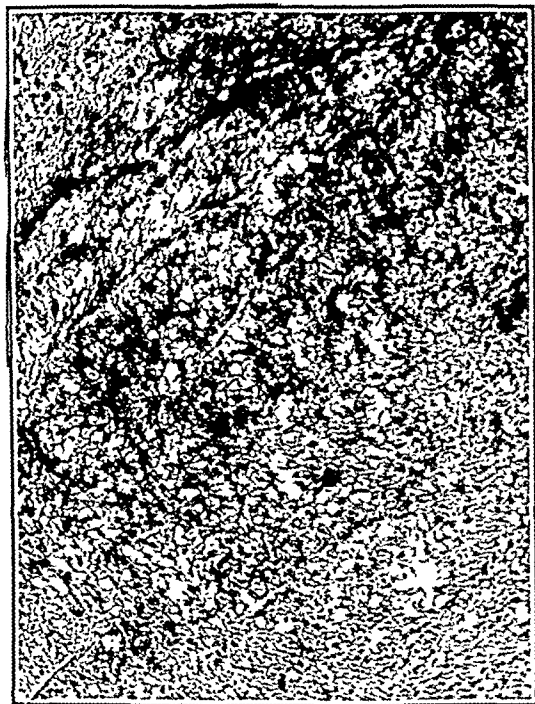


FIG. 3. Section of Myocardium (x 100).



FIG. 4. Section of Brain (x 100).

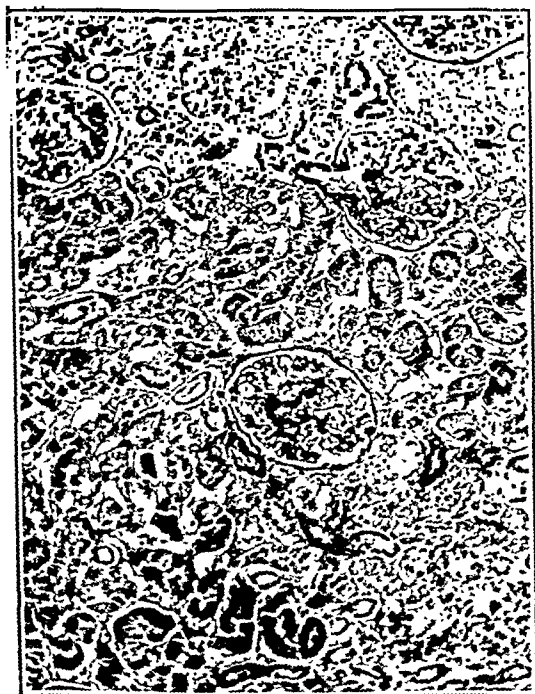


FIG. 5. Section of Kidney (x 100).

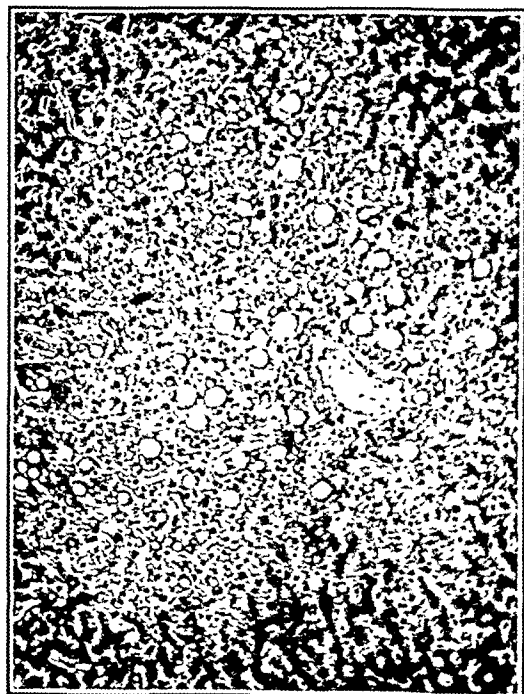


FIG. 6. Section of Liver (x 100).

was swollen with edema, some fields showing necrosis. There was a heavy cellular infiltration into the mucosa consisting of polymorphonuclear cells and of various types of the monocytic series. The bronchial muscle fibers were swollen and pale, many appearing to be in the early stage of coagulation necrosis. The glands of the bronchial mucosa were distended with secretion and showed heavy cellular infiltration.

In the *lungs* there was widespread acute congestion. The site of each bronchiole was marked by an intense inflammatory reaction, loosening or desquamation of the bronchiolar epithelium and filling of the lumina with cellular debris. Under the displaced epithelium there were dense cellular infiltrations of polymorphonuclear and other leukocytes which extended out into the adjacent lung structure, constituting an acute peribronchiolar pneumonia with breakdown of alveolar walls and filling in to form small coalescent alveolar abscesses. The small blood vessels were greatly congested and frequently showed a perivascular collar of leukocytes.

Sections from the interventricular septum of the *heart* showed interstitial edema of the myocardium. Many groups of muscle fibers showed hyalinization, a "curling" misshaping, swelling or acute atrophy and, in some fields, infiltration by leukocytes. There was intimal thickening in the left coronary artery.

The *brain* disclosed occasional foci throughout the white matter where the original structure had disappeared or was in process of doing so. These areas took a pale reddish stain and gave the appearance of fibrinous necrosis. However, there was no hemorrhage into these acutely necrotic areas. Many small blood vessels, venules and possibly some arterioles were filled with hyaline thrombi completely occluding the vessels.

There was marked congestion of the *renal* glomeruli. While the capsules were distended and, in many glomeruli, showed slight to moderate thickening, there was no regular inflammatory reaction. All of the proximal convoluted tubules showed marked epithelial swelling, almost closing the lumina in many instances and constituting a marked nephrosis. In contrast to this the distal tubules were well preserved although they contained much albuminous and hemoglobinuric material.

The inner third to half of each *liver* lobule showed much fatty change, whereas the outer half was markedly congested. In the interlobular capillaries were seen a greater number of leukocytes than normal. There was an occasional swollen Kupffer cell and slight to moderate infiltration of leukocytes in the perilobular connective tissue. The nuclei of

the hepatic cells were in general well preserved, except in the areas of marked fatty degeneration.

In the upper *gastrointestinal tract* the squamous epithelium of the esophagus was generally intact but the mucosa was swollen with distended capillaries, marked interstitial edema and leukocytic infiltration. The muscular layers all showed some swelling due to interstitial edema. Unfortunately, sections from the stomach were lost. The duodenum showed acute focal necrosis of the epithelium and a marked inflammatory reaction in the mucosa and submucosa.

The *adrenals* revealed medullary edema and focal degeneration in the cortex. There was hyperplasia of the *splenic pulp* with congestion and hemorrhage.

The *pathological diagnosis* was acute ulcerative tracheobronchitis, bronchiolitis and bronchiolar pneumonia, with secondary toxic changes in the heart, kidney and liver; acute esophagitis; acute gastritis; acute duodenitis.

**Discussion.** For a specific toxicologic diagnosis it would, of course, be desirable to have identified the presence of diazomethane in the blood stream or the tissues of the patient. However, the great instability and the high reactivity of the poison as well as the time which elapsed between exposure and the conclusion that diazomethane was the responsible agent, a matter of some 72 hours, made such a procedure entirely unfeasible. Furthermore, there is apparently no test available at this time by which such an identification could be made.

Sunderman's patient<sup>10</sup> gave an unquestionable history of hay fever and asthma. The manifestations which he exhibited resembled those of bronchial asthma so strongly that therapy early in the course of that patient's illness was directed along those lines. In the present case there had never been any allergic phenomena during the patient's lifetime. The clinical appearance was that of a fulminating pneumonia. The reason for the difference in the manifestations is open to question. The degree and duration of exposure to diazomethane is without doubt of considerable importance. Of great moment,

also, is the mode of action of this agent. Due to its high reactivity it combines readily with the tissues. In the present case it is probable that the intense involvement of the tracheobronchial tree was due to direct contact with inhaled gas while the pronounced gastrointestinal changes were possibly similarly due to contact with the diazomethane-contaminated sandwich eaten while the patient worked in the laboratory. It is of great interest to note that there was no complaint of dysphagia at any time.

Flury and Zernik<sup>4</sup> state that there is a slow reaction of diazomethane with water to form methyl alcohol, with the liberation of nitrogen. Oxidation of methyl alcohol produces formaldehyde. Lehmann and Flury<sup>7</sup> point to the formation of formaldehyde and formic acid from methyl compounds, such as diazomethane, and include these substances among the true enzyme poisons. Axmacher<sup>3</sup> has found that diazomethane inactivates zymase as well as carboxylase in yeasts. From these statements it seems probable that it has a similar effect on enzyme systems in animal tissue.

In areas such as the trachea the action of diazomethane appears to be corrosive, at least in part. However, its influence on tissues where there has been no direct contact cannot be of this character. Landsteiner and DiSomma<sup>6</sup>, who employed diazomethane as a sensitizing agent in order to produce allergic effects, noted that the reactivity of this poison is so great "that it doubtless combines with substances of the animal body rapidly after administration and for this reason the spread of sensitization can hardly be ascribed to the distribution of the exciting substance itself but to transportation of some sort of conjugate (such as methylated protein) or, perhaps, antibodies".

In a discussion of the industrial hazards presented by organic chemical synthesis Watrous<sup>11</sup> points out that the active agents used to attack and modify the structure of organic compounds are, by their very nature, exceptionally able to modify the organic compounds of the human body, thus producing highly poisonous effects. Watrous also notes that the intermediate compounds in most organic syntheses are often characterized by the readiness with which they enter into chemical combination with other organic matter; they are active. This frequently confers toxic properties of great variety upon them. Of great importance is the fact that any investigator who works with diazomethane, or any other agent such as Watrous describes, is employing a powerful and deadly chemical. It behooves those who supervise laboratory procedures to be aware of the dangers inherent in the activities of their students or assistants and to give full and adequate emphasis to those dangers when any hazardous project is undertaken.

**Summary.** A report of the clinical features and autopsy findings in a case of poisoning by diazomethane has been presented. Diazomethane is a highly toxic agent which appears to have a corrosive action upon tissues with which it is in direct contact. In addition, it appears to produce sensitizing effects so that part of its insidious character lies in allergic reactions which may arise in any area or organ of the body not directly exposed to it. The clinical picture thus produced may resemble bronchial asthma or a fulminating pneumonia. The great caution necessary on the part of those who work with this agent is clearly evident and should be stressed whenever its use is contemplated.



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# THE DIAGNOSTIC SIGNIFICANCE OF "BURR" RED BLOOD CELLS\*

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IN the course of the routine review of blood films a peculiar red cell, measuring about 7.5 micra or less in diameter and having one or more large spiny projections along its periphery, was seen from time to time. The impression was gradually gained that this form represented an entity which, although occasionally encountered in other conditions, occurred most frequently in uremia, carcinoma of the stomach, and peptic ulcer with bleeding. We have found that this peculiar poikilocyte, which we have designated "burr" cell, often offers the first clue to diagnosis. Experience has taught us to use "burr" cells as valuable signposts in the etiologic evaluation of anemias. This study was undertaken to test the validity of what, to the present time, had been simply an impression, and to determine the frequency with which "burr" cells occur in both normal and abnormal states.

**Material and Methods.** Blood films from 75 cases of uremia, 50 cases of carcinoma of the stomach, and 50 cases of bleeding peptic ulcer were studied. The control series was made up of 2 groups. The first consisted of 100 consecutive blood films obtained from patients entering the medical wards of the hospital for miscellaneous conditions and having no hematologic aberrations, while the second was made up of 100 similarly obtained bloods which showed some hematologic abnormality such as anemia, leukocytosis, poikilocytosis, and so on.

The diagnosis of uremia was made on the basis of azotemia together with one or more of the clinical findings of nausea, vomiting, irritability, lethargy, uremic frost, pericarditis, and coma. All patients had blood creatinine levels of 3 mg. per 100 cc. or over and non-protein-nitrogen levels of 70 mg. per 100 cc. or more. Of the 75 patients whose bloods were studied, 71 died. The blood pressure was 150/90 or over in 62 (82%) of these cases.

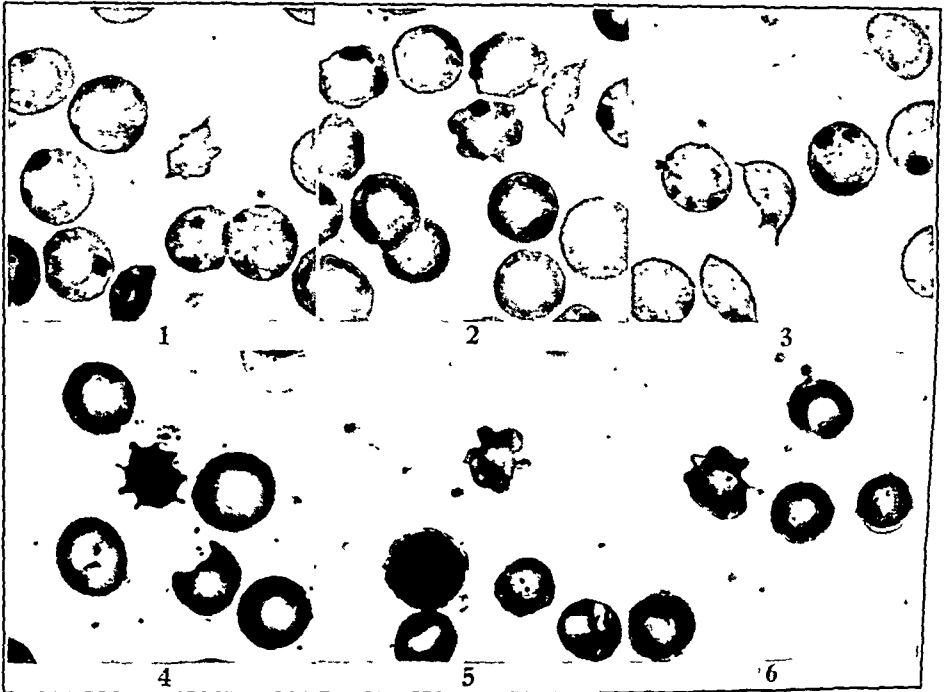
The diagnoses of carcinoma of the stomach and bleeding peptic ulcer were substantiated by gastroscopy, Roentgen-ray, and, or, surgery.

One thousand red blood cells were counted on each dry blood film. In addition, 25 wet preparations were made; 15 from the blood of uremic patients, 5 from patients with carcinomas of the stomach, and 5 from patients with bleeding peptic ulcers, in order to study the appearance of the cells in a relatively unmodified state.

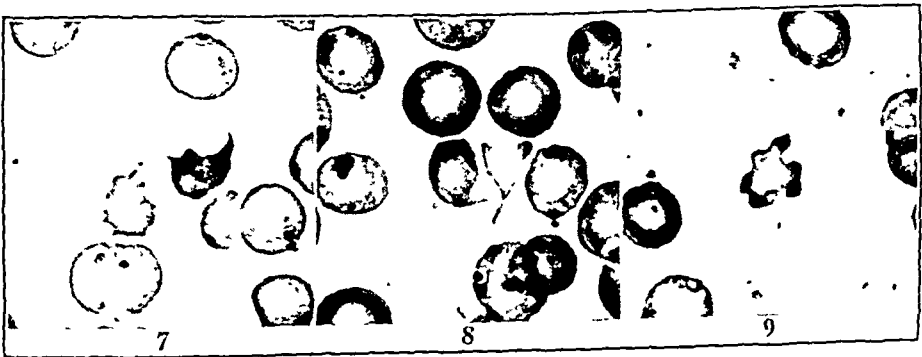
We were particularly interested in determining whether the "burr" cell was a form of poikilocyte or a crenated cell. The appearance and frequency of occurrence of the "burr" cell in the wet preparations leaves little doubt but that these cells represent a preformed poikilocyte and not a crenated cell. There are occasional "burr" cells, however, which are difficult to differentiate from crenated cells (Figs. 2 and 9).

The "burr" cell is a mature erythrocyte about 7.5 micra or less in diameter, which has one to several spiny projections along its periphery. We have

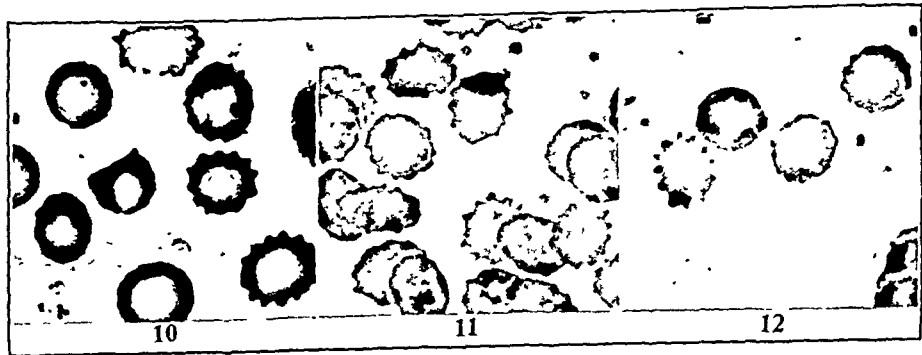
\* Aided by a grant from the Wilson Laboratories, Chicago, Illinois.



Figs. 1 to 6. Various kinds of "Burr" cells.



Figs. 7 to 9. Various kinds of "Burr" cells  
(Cont'd)



Figs. 10 - 12. Crenated Erythrocytes.

chosen to call it "burr" cell because of its resemblance to the prickly envelope of a burr. "Burr" cells differ from crenated red cells in that the latter have many, fairly symmetrically arranged small spiny projections which often occur on the surface as well as the periphery; and whereas crenated cells occur in groups, sometimes more in one area than another, "burr" cells are fairly evenly scattered throughout the blood film. In the enumeration of "burr" cells for this study only those were counted which were untouched by adjacent cells and which were located in fields in which no crenated cells were present.

Of the 75 cases of uremia, 54 cases (73%) showed "burr" cells. The range of incidence of the "burr" cell in this group was 0.1% to 1.5% (1 to 15 "burr" cells per 1,000 red cells counted). No correlation existed between the incidence of "burr" cells and race, sex, age, height of blood pressure, anemia, color index, or the levels of the non-protein-nitrogen or creatinine.

Of the 50 patients with carcinoma of the stomach, 34 (68%) had "burr" cells. The percent incidence of the "burr" cell in this group was from 0.1 to 3.7 (1 to 37 "burr" cells per 1,000 red blood cells counted). No correlation was demonstrable between the incidence of "burr" cells and race, sex, age, and the anemia or the color index.

Of the 50 patients with bleeding peptic ulcers, 27 (54%) showed "burr" cells. The range of the incidence of "burr" cells in this group was 0.1% to 1.2% (1 to 12 "burr" cells per 1,000 red cells counted). In this series there were 37 patients with duodenal ulcers, 11 with gastric ulcers, and 2 with marginal ulcers. No correlation existed between "burr" cell incidence and the site of the ulcer, race, sex, age, anemia or the color index.

On the 100 blood films of the control group which revealed miscellaneous

non-hematologic diseases, no "burr" cells were found; while in the 100 preparations obtained from patients showing some hematologic aberration, 21 had "burr" cells. The 21 cases were made up of the following conditions:

|   |   |
|---|---|
| Azotemia                                    | 8 |
| Organic Heart Disease                       | 1 |
| Organic Heart Disease with Failure          | 2 |
| Carcinoma—Rectum                            | 2 |
| Carcinoma—Gastro-intestinal—site unknown    | 2 |
| Carcinoma-stomach                           | 1 |
| Pernicious Anemia                           | 1 |
| Pernicious Anemia—with Carcinoma of Stomach | 1 |
| Malnutrition                                | 1 |
| Tuberculosis                                | 1 |
| Thyrototoxicosis                            | 1 |

**Discussion.** This study failed to reveal the pathogenesis of the "burr" red cell and did not elucidate the common denominators among uremia, carcinoma of the stomach, and bleeding peptic ulcer. Severity of anemia, level of color index, amount or duration of bleeding, degree of nitrogen retention, age, sex and race were all taken to be insignificant. Hypoproteinemia and blood in the intestinal tract may play a part. Dehydration is apparently not a significant factor, as we have not commonly observed "burr" cells in severely dehydrated diabetic patients in acid-

TABLE 1. OCCURRENCE OF "BURR" CELLS IN THE CONDITIONS STUDIED

| Condition                          | Number of Cases | Incidence of "Burr" Cells |         | Range of Incidence of "Burr" Cells |
|------------------------------------|-----------------|---------------------------|---------|------------------------------------|
|                                    |                 | Number                    | Percent |                                    |
| Normal                             | 100             | none                      | 0       |                                    |
| Various hematologic abnormalities* | 100             | 21                        | 21      | —                                  |
| Uremia                             | 75              | 54                        | 73      | 0.1%—1.5%                          |
| Carcinoma of stomach               | 50              | 34                        | 68      | 0.1%—3.7%                          |
| Bleeding peptic ulcer              | 50              | 27                        | 54      | 0.1%—1.2%                          |

\* These include an undetermined but probably small number of cases of uremia, carcinoma of the stomach, nephritis, and so on.

osis. It is interesting that in the control group of miscellaneous hematologic conditions the most frequent common denominator was renal impairment.

**Summary.** In the peripheral blood of patients with uremia, carcinoma of the stomach, and bleeding peptic ulcer, peculiar poikilocytes frequently occur which we have designated as "burr" cells.

"Burr" cells occurred in the bloods of

73% of the patients with uremia, 68% of carcinoma of the stomach, and 54% of bleeding peptic ulcers.

"Burr" cells are very rare in normal bloods (none in 100 control cases), but occur in conditions other than the above mentioned—though their presence should always suggest additional renal involvement.

**Conclusion.** "Burr" cells are valuable sign posts in the study of anemias.

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## RECENT ADVANCES IN PARENTERAL FLUID THERAPY

With Ammonium Chloride and Potassium

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THE field of parenteral fluid therapy has been developed chiefly during the past 25 years. General progress in the fields of biochemistry and physiology as well as more specific investigations on fluid and electrolyte metabolism have supplied a basis for the rational use of such solutions as saline, glucose, sodium bicarbonate, and sodium lactate in the treatment of dehydration and acid-base disturbances. The literature contains a number of excellent reviews which summarize these basic studies and therapeutic procedures<sup>1,10,36,78</sup>. During the past few years a number of other substances, namely, ammonium chloride, potassium salts, protein digests and whole blood have assumed importance in parenteral therapy. It is the purpose of the present paper to review the advances in the fields of

ammonium chloride and potassium therapy.

**Potassium.** Until about a decade ago, it was generally assumed that such ions as sodium and chloride were extracellular, that others such as potassium and magnesium were predominantly intracellular, and that there was little exchange of these various ions across the cell wall. The work of Hastings, Eichelberger and their associates<sup>23,48,49,70</sup> on the calculation of the extracellular and intracellular phases of muscle tissue were based on such assumptions and the results of their work substantiated these assumptions. However, Hastings carefully pointed out at this time that these assumptions held under essentially normal physiological conditions. During the past decade there has accumulated increasing

evidence that the cell wall is not as impermeable as it was formerly thought to be and that under unusual environmental or pathological conditions, intracellular electrolytes may pass across the cellular membranes and, on the other hand, that under appropriate therapeutic conditions such intracellular components may be restored. Some information concerning the normal distribution and metabolism of potassium in the body is necessary before we consider the deviations in disease and the therapeutic measures necessary to correct these deviations. As for any other component of the body, it is important to determine the relationship between the extent of storage and excretion throughout a wide range of various levels of intake, and to ascertain the influence of various physiological variables upon this relationship.

**DISTRIBUTION OF POTASSIUM IN THE HUMAN BODY.** The potassium content of the human body has been estimated variously as anywhere between 0.11 to 0.35%.<sup>95</sup> This would mean that an individual weighing 70 kg. would contain between 77 and 245 gm. or between about 2000 to 6000 m.Eq. of potassium. Myers and Mangun<sup>80</sup> found that the pectoralis major muscle contained an average of 352 mg. potassium per 100 gm. tissue; if a similar estimate is made of the potassium content of other tissues, then the total content in a 70 kg. adult would be about 245 gm.

The normal concentration of potassium in the blood serum of man is about 16 to 20 mg. per 100 cc. or about 4 to 5 m.Eq. per liter. Thus, in a series of 10 normal individuals Kramer and Tisdall<sup>61</sup> found the serum potassium to range from 19.2 to 20.0 and average 19.6 mg. per 100 cc. Hald and Eisenman<sup>46</sup> observed a somewhat greater variability in a series of 16 normal individuals; the concentration ranged from 3.4 to 6.5 and averaged 4.6 m.Eq.

per liter. Recently, in a series of flame photometric determinations on 106 normal individuals, Marinis and his associates<sup>72</sup> found the values to range between 3.6 and 6.2 m.Eq. per liter. Of these values 75% fell between 4.2 and 4.8 m.Eq. per liter and 93% between 3.9 and 5.1 m.Eq.

The concentration of intracellular potassium cannot, except in the case of the red blood cells, be determined directly. However, the concentration of potassium in the red cell can also be determined indirectly. In the series of 16 individuals previously referred to, Hald and Eisenman found the concentrations of potassium in the red cell to range from 72 to 102 and average 83 m.Eq. per liter or about 125 m.Eq. per liter of intracellular water. In order to calculate the intracellular potassium content of other tissues, it is necessary to determine the potassium content of the whole tissue, then from this value subtract the amount of potassium in the extracellular compartment of the tissue. The latter is calculated on the assumption that the extracellular fluid comprises about 15 to 20% of the tissue and that the concentration of potassium in the extracellular fluid is the same as that in the plasma, but corrected for the Donnan effect. Katz<sup>55</sup> found a concentration of 320 mg. and Myers and Mangun<sup>80</sup> 352 mg. of potassium per 100 gm. of human muscle. This is of the same order of magnitude as that recently reported by Mudge and Vislocky<sup>79</sup>, namely, 82 to 88 m.Eq. per kg. of fat-free tissue. These values yield a concentration of about 150 to 160 m.Eq. per liter of intracellular water.

**METABOLISM OF POTASSIUM.** The normal daily potassium intake and excretion of an adult is about 3 to 4 gm. or 75 to 100 m.Eq.<sup>26,95</sup>. Practically the entire excretion takes place through the urine and feces, although there is evidence that potassium is also eliminated

through the perspiration. Estimations of the excretions are, however, usually based on urine and stool analyses; it is found that about 10 to 20% of the potassium is excreted in the stools, and the remainder in the urine. These statements may be illustrated by reference to specific studies. For example, Bassett and his associates<sup>4</sup> found, in one instance, that on an average daily intake of 3.79 gm., the excretion was 3.19 gm.; of this amount 14% was in the stools. In their series of classical studies on chemical growth in children, Macy and her co-workers<sup>68</sup> found that, in children ranging from 4 to 12 years of age, the excretion ranged from about 90 to 96% of the daily intakes, 2.5 to 3.5 gm. The fecal excretion ranged from 8 to 16% of the total excretion.

There appear to be only a few studies which indicate the minimal intake of potassium that is necessary on a complete and adequate diet to keep the body in potassium balance. Fasting adults who receive water may excrete daily from 30 to 76 m.Eq. (1.2 to 3.0 gm.) of potassium<sup>22, 109</sup>. Tarail and Elkin<sup>103</sup> found that the daily loss of potassium was of about the same order, 49 to 53 m.Eq., when a normal individual was on a calorically adequate but practically potassium free diet. On adequate daily diets containing 99 to 116 m.Eq. of potassium per day, 2 normal individuals showed balances ranging from -30 to +13 m.Eq. per day. It would be of value to obtain additional balance data in normal individuals at intermediate potassium intakes.

**LOSS OF INTRACELLULAR POTASSIUM IN DISEASE.** In 1933, Butler, McKhann, and Gamble<sup>9</sup> observed that infants who had been suffering from severe diarrhea excreted, during the first 24 hours after being placed on glucose and saline, more potassium than could be accounted for on the basis of tissue destruction, as measured by the excre-

tion of nitrogen. The losses of intracellular water, calculated on the basis of nitrogen excretion, were less than those calculated on the basis of the amounts of potassium excreted. These findings indicated that potassium and water were leaving the cells.

These findings were established again by Darrow<sup>18</sup> in 1946. When infants with diarrhea were admitted to the hospital and placed on parenteral fluid therapy consisting of solutions of saline, lactate, glucose and of blood, there occurred marked negative potassium balances. Correction for the amount of potassium resulting from tissue breakdown showed that potassium was migrating out of the cells. When potassium chloride was added to the diet in the next metabolic period, a marked positive balance of potassium resulted. For example, in one case, the potassium balance was -8.43 m.Eq. during a 39.5 hour metabolic period on the usual parenteral fluid therapy. When 2 gm. of potassium chloride were given during the next metabolic period of 49.5 hours, the potassium balance was positive to the extent of 23.1 m.Eq. We shall consider presently the other significances of this uptake of potassium, but it may be noted here that such uptake was further indication that the cells had been depleted of potassium.

Darrow's observations and penetrating inferences<sup>18, 19</sup> have been followed by a number of other reports which demonstrate the passage of potassium across cellular membranes in other diseases or in marked physiological derangements. Danowski and his associates<sup>15</sup> have shown that in familial periodic paralysis the onset of episodes of paralysis is associated with a transfer of potassium from the extracellular to the intracellular phase, resulting in a sharp decrease in the concentration of potassium in serum and presumably also in the extracellular phase. Elkin-



ton, Tarail and Peters<sup>24</sup> have observed that occasionally in patients with renal insufficiency and hyperpotassemia, potassium may be taken up by the cells. It had also been shown that in animals, diets low in potassium<sup>32, 50, 77</sup>, injections of desoxycorticosterone acetate<sup>20, 29</sup>, estradiol benzoate or testosterone propionate<sup>76</sup> cause a reduction in the potassium content of muscle.

In the clinical conditions which we mentioned above, the interchanges of intracellular potassium were demonstrated indirectly by balance studies. There are, however, a few direct analyses of the potassium content of muscle which support these conclusions. Darrow reported that in babies dying of diarrhea the potassium content of muscle was about 40% less than that of normal muscle<sup>18</sup>. Mudge and Vislocky<sup>79</sup> analyzed biopsy specimens and found that the contents of potassium in the muscle of 3 patients with renal acidosis were 74.5, 69.1 and 66.1 m.Eq. per kg. of fat-free tissue. In 3 patients with gastric alkalosis, the concentrations ranged from 51.4 to 85.7 m.Eq. per kg. These were lower than the values from 3 normal individuals, namely, 81.9, 87.0 and 88.0 m.Eq. per kg.

**RELATIONSHIP BETWEEN SODIUM AND POTASSIUM INTERCHANGES.** A number of investigators have shown that an interrelationship exists between sodium, potassium, chloride and bicarbonate ions. When the muscle potassium in rats was decreased by feeding a diet low in potassium or by injecting desoxycorticosterone acetate, the concentration of intracellular sodium rose<sup>21</sup>. Simultaneously, the concentration of bicarbonate in the extracellular phase (plasma) rose and that of chloride declined. When acidosis was produced, the intracellular sodium increased.

In general, then, serum bicarbonate varied directly with the intracellular sodium and inversely with the intra-

cellular potassium. Fox and Baer<sup>24</sup> found that when the hind leg of a mouse was injured by tourniquet trauma or by scalding, the injured leg lost a considerable amount of potassium but gained sodium. Conversely, the opposite uninjured leg lost sodium but gained potassium. The direct analyses of Mudge and Vislocky<sup>79</sup> on human muscle show that in acidosis and alkalosis the concentration of intracellular sodium rises as the concentration of intracellular potassium decreases. Thus, whereas the normal concentration of sodium ranged from 2 to 14 m.Eq. per liter of intracellular water, concentrations from 17 to 40 m.Eq. per liter were obtained in acidosis and from 13 to 74 m.Eq. per liter in alkalosis.

The interdependence between potassium, sodium and bicarbonate ions has also been observed clinically. A few instances of this may be cited in illustration. McQuarrie, Johnson and Ziegler<sup>67</sup> reported a case of Cushing's disease which had a CO<sub>2</sub> combining power of 112 vols. per 100 cc. and a pH of 7.55 to 7.60. The concentrations of the other ions (as read from the author's Chart) were as follows per liter: Na<sup>+</sup>, 155 m.Eq.; K<sup>+</sup>, 2 m.Eq.; HCO<sub>3</sub><sup>-</sup>, 42 m.Eq.; Cl<sup>-</sup>, 88 m.Eq. In another instance of Cushing's disease, Willson, Power and Kepler<sup>108</sup> observed the following ionic concentrations per liter: Na<sup>+</sup>, 137 m.Eq.; K<sup>+</sup>, 2.2 m.Eq.; HCO<sub>3</sub><sup>-</sup>, 46 m.Eq.; Cl<sup>-</sup>, 78.0 m.Eq. Recently, it has been shown that after operation, hypopotassemia may occur accompanied by an increased concentration of bicarbonate ion in the serum<sup>53, 64, 66, 83</sup>.

**HYPOPOTASSEMIA AND HYPERPOTASSEMIA.** As we have already seen, balance studies can yield a fairly precise idea concerning the existence of intracellular potassium deficits. Since only about 10 to 20% of excreted potassium is found in the stools, determinations of urinary excretion of potassium may

also serve as a valuable, though only approximate, guide of undue losses or of storage of potassium in the body. However, since the blood is most readily available for analysis, it is of interest to determine the extent to which the level of potassium in the serum can serve as an index of intracellular potassium deficits.

A lowered concentration of serum potassium has been found in patients recovering from diabetic acidosis<sup>35,52,65,82,104</sup>, in infantile diarrhea<sup>91</sup>, alkalosis due to intestinal obstruction and vomiting<sup>5</sup>, congenital alkalosis with diarrhea in early life<sup>17,38</sup>, periodic paralysis<sup>2,27,28,40,41,99,105</sup>, nephritis<sup>8,87,96,103</sup> and in postoperative states<sup>53,64,66,83</sup>. It will be recalled that most normal values for the concentration of serum potassium range between 4 and 5 m.Eq. In familial periodic paralysis, values of between 2 and 3 m.Eq. per liter have often been recorded. Logsdon and McCavack<sup>65</sup> have reported a value of as low as 1.0 m.Eq. in a patient with diabetic acidosis who developed respiratory paralysis and died. In renal insufficiency, the concentration of serum potassium may be either low, normal or high. Elkinton and his associates<sup>24</sup> found that of 26 patients with renal insufficiency, 4 had serum potassium concentrations less than 3.5 m.Eq. per liter, 23 had concentrations between 3.5 and 6.4 m.Eq. per liter, and 11 showed values greater than 6.4 m.Eq. per liter.

The concentration of potassium in the serum represents the resultant of several processes, namely, introduction of potassium into the organism, liberation from or storage in the tissues, and excretion through the urine or stools. It does not necessarily follow, therefore, that a low concentration of serum potassium will be obtained when there is a low store of intracellular potassium. In the 6 cases of infantile diar-

rhea studied by Darrow<sup>18</sup>, the initial potassium concentrations were 7.4, 6.7, 5.0, 5.5, 4.8, and 3.7 m.Eq. per liter. Some of these results are high and, as will be seen later, may indicate renal impairment. Yet these patients had been losing potassium, continued to do so when placed on saline-glucose therapy, and presumably, therefore, had intracellular potassium deficits. Rapoport and his associates<sup>88</sup> found that when the acidosis of infantile diarrhea was corrected by the administration of sodium bicarbonate, there occurred marked decreases in the concentration of potassium, as well as calcium and phosphorus. Decreases of the potassium concentration to between 2 and 3 m.Eq. per liter were common and occasionally values below 2 m.Eq. per liter were obtained. They interpreted this finding to indicate an avid uptake of these ions by the previously depleted tissues. Although Rapoport and his co-workers reported no balance studies, it may be appreciated that his interpretations are in accord with the observations and conclusions later established by Darrow. In the extremely rare condition of congenital alkalosis with diarrhea studied by Darrow<sup>17</sup>, low concentrations of serum potassium were obtained occasionally. The metabolic results showed that there was an excessive excretion of potassium in the urine and stools, and suggested that the initiating force for this excretion was the driving out of potassium from the cells and its replacement by sodium.

The genesis of hypopotassemia in diabetic acidosis has been investigated by Danowski and co-workers<sup>16</sup>. The classical studies of Atchley, Loeb, and their associates<sup>3</sup> had shown that during the development of insulin-withdrawal acidosis, there was a marked diuresis of large amounts of potassium, nitrogen, phosphorus and other elements. In one case studied by these investigators, there was a net loss of

385 m.Eq. potassium during a 4 day period of acidosis. This is about 10% of the total store in the body. Danowski and associates<sup>16</sup> found that when the conventional therapy of insulin, glucose, and saline was administered to patients with diabetic acidosis, there occurred a rather sizable increase in the extracellular fluid volume of the body while at the same time potassium continued to be excreted from the body. For example, in a female diabetic weighing 50 kg., 74 m.Eq. of potassium were excreted during a 20 hour period on insulin, saline and glucose therapy. The extracellular fluid volume increased by 4.4 liters or by about 8% of the body weight. The hypopotassemia of post-acidotic diabetes may accordingly be ascribed in part to a continued loss of potassium from the body, and in part to a dilution of the potassium ion as a result of the increased extracellular fluid volume.

The extraordinary depletion of potassium which the cells of the body undergo during the development of diabetic acidosis and treatment with parenteral fluids devoid of potassium is manifested by an equally unusual retention which occurs when potassium is administered to such patients. For example, in the case quoted above, Danowski and associates<sup>16</sup> found that the administration of 505 m.Eq. of potassium during a 47 hour treatment period resulted in the retention of 297 m.Eq. Of this amount, 292 m.Eq. were deposited intracellularly. Howard and Carey<sup>53</sup> note an instance in which they injected 467 m.Eq. of potassium (35 gm. KCl) into a patient with diabetic acidosis in 18 hours; less than 100 m.Eq. of potassium were found in the urine. Tarail and Elkinton<sup>103</sup> showed that, in contrast, normal individuals retained only 5 to 10% of a dose of 250 m.Eq. of potassium.

It has been shown that the glomerular filtration and the renal excretion

of potassium may be decreased in patients with renal insufficiency. Whether the concentration of serum potassium in this condition increased or not depends upon a number of factors, namely, the intake of potassium, the extrarenal loss of potassium, the decreased renal excretion of potassium, the change in the volume of the extracellular fluid, and the interchange of potassium between the extracellular and intracellular phases<sup>24</sup>. Certainly it would appear that in those cases in which hyperpotassemia occurs, the factor chiefly responsible is the decreased renal excretion of potassium. Hyperpotassemia of this type does not favor intracellular deposition; of 9 cases studied by Elkinton and associates<sup>24</sup> on daily intakes ranging from 0 to 30 m.Eq., 7 showed losses of intracellular potassium and only 2 showed slight deposition. The occurrence of decreased concentrations of serum potassium in patients with renal insufficiency is to be ascribed chiefly to the fact that although the renal excretion is decreased, the intake is limited because of anorexia, chiefly for foods containing potassium, and losses occur through the gastrointestinal tract.

The hypopotassemia in familial periodic paralysis appears to have an entirely different cause from those described above. It is, of course, well known that hypopotassemia in this condition with accompanying episodes of paralysis is induced by the administration of insulin, epinephrine or carbohydrate<sup>41</sup>. Why such stimuli should produce the hypopotassemia in patients with periodic paralysis but not in normal individuals is not well understood. Danowski and his associates<sup>16</sup> have shown that the episodes of paralysis are associated with small transfers of potassium from the extracellular to the intracellular phase. For example, in 1 patient in whom paralysis was induced by the administration of a potassium

free carbohydrate diet, the serum potassium decreased progressively from 4.3 to 2.2 m.Eq. per liter. The intracellular entrance in several metabolic periods of 5 to 24 hours duration ranged from 5 to 20 m.Eq., approximately equal to a decrease of about 2 m.Eq. per liter in the 15 liter extracellular fluid volume of the patient.

It is abundantly evident from the few examples which we have given that the concentration of potassium in the serum may, but does not necessarily, reflect the stage of depletion or repletion of intracellular potassium. To illustrate and summarize, the serum potassium is not low and indeed may be high in the active stage of infantile diarrhea where the potassium has left and is still leaving the cells. But in the tissue depletion of congenital alkalosis with diarrhea, it may occasionally be low, and in the postacidotic phase of infantile diarrhea, ingress from the extracellular fluid to the depleted cells leads very frequently to decreased concentrations of serum potassium. The hypopotassemia of the postacidotic phase of diabetes mirrors well the extreme cellular depletion in this condition, but the hypopotassemia of familial periodic paralysis is due to some curious fault whereby some of the extracellular potassium, but enough to lower the concentration in the serum, is rather suddenly deposited in the intracellular phase. As we have seen, the situation in renal impairment is somewhat more complex. It may be appreciated that an understanding of the biochemical mechanism underlying the relations of serum and intracellular potassium in each disease is essential for the proper therapeutic employment of potassium.

**CLINICAL SYMPTOMS OF POTASSIUM DEFICIENCY.** As we have seen, the existence of a potassium deficiency can be ascertained with considerable precision by balance studies and biochemical

analysis of the serum. However, opportunities for conducting balance studies are available in only a few hospitals. The precise chemical determination of serum potassium is a painstaking and time-consuming procedure, although the recent use of the flame photometer has facilitated such determinations greatly. It is, therefore, necessary in many instances to judge the existence of a potassium deficiency on the basis of history and clinical symptomatology.

In the earlier stages of potassium deficiency, the patient shows a loss of strength and energy and is listless<sup>64</sup>. Many of the patients are unable to eat adequate amounts of food. This symptomatology is obviously common to a great many conditions and diseases. The manifestations of marked potassium deficiency are more distinctive<sup>53</sup>. Weakness of the extremities becomes marked; flaccid paralysis, sometimes of the ascending or Landry's type, may then ensue. There is rarely any involvement of the trunk or cranial nerves. Weakness of the respiratory muscles is a grave symptom<sup>35,52,65</sup>. The breathing becomes rapid and shallow and the symptoms of gasping for air, namely, use of accessory muscles, retraction of head and neck, dilatation of alae nasi with each respiration, and "fish mouth" type of breathing become evident. There is very little movement of the chest wall and diaphragm. In the absence of prompt potassium therapy, respiratory paralysis and death may ensue.

The changes in the electrocardiogram associated with abnormalities of the concentration of serum potassium have received considerable attention<sup>30, 57,98,101,102,110,111</sup>. Winkler, Hoff and Smith<sup>110</sup> found the following changes upon the intravenous infusion of isotonic potassium chloride into dogs: increase in the amplitude of the T wave at serum potassium concentrations

ranging from 5.0 to 7.8 m.Eq. per liter, depression of the S-T segment at 8 to 10 m.Eq. per liter, intraventricular block at about 10 m.Eq. per liter, disappearance of the P wave at 9 to 11 m.Eq., and cardiac arrest at 14 to 16 m.Eq. per liter. The changes in man parallel, in general, those found in animals. As the serum potassium rises, there is first an increase in the amplitude of the T wave; then a decrease in the amplitude of the R wave with an increase in the amplitude of the S wave. At higher concentrations, there is a disappearance of the P wave, a depression of the RS-T segment and a widening of the QRS complex. There is incomplete accord, however, with regards to the concentrations of serum potassium at which these changes occur. Winkler, Hoff and Smith<sup>111</sup> as well as Tarail<sup>101,102</sup> found that in patients with uremia and concentrations of serum potassium ranging from 6.8 to 8.3 m.Eq. per liter, the most characteristic changes were peaked T waves and an increase in the duration of the QRS complex. Finch and his co-workers<sup>30</sup> observed disappearance of P wave at between 9 and 9.5 m.Eq. per liter and spread of QRS complex at between 9.5 and 10.5 m.Eq. per liter. Stewart and his associates<sup>98</sup> reported 2 cases with concentrations of 10.3 and 10.6 m.Eq. per liter in whom there was disappearance of the P waves and widening of the QRS complexes.

In hypopotassemia, the sequence of electrocardiographic changes is as follows. With moderate decreases, the T wave becomes slightly lower but broader, so that the Q-T interval as a whole is lengthened. As the serum potassium concentration is decreased further, there is first a lowering or inversion of the T wave and then a sagging of the ST segment. With very low levels of potassium (1.5 m.Eq. per liter or less), there is a slow, staircase-like rise to a low late T wave<sup>53</sup>.

It must be emphasized that the relationship between the level of potassium and the electrocardiographic changes is only approximate. For example, in a series of patients with diabetic acidosis, Martin and Wertman<sup>73,74</sup> observed that at normal serum potassium levels (4.2—5.8 m.Eq. per liter), 14 showed a normal amplitude of T waves, 12 a decreased amplitude, and 1 a very low T wave. At serum potassium levels less than 4.2 m.Eq. per liter, 1 showed a normal amplitude of T waves, 1 a decreased amplitude, and 9 a very low amplitude. In a similar series, Nadler and his associates<sup>81</sup> observed an approximate but a statistically significant correlation between the prolongation of the Q-T interval and the decrease in the serum potassium. However, a significant correlation could also be shown to exist between the height of the T wave and the pH of the serum.

It is apparent that the proper use of electrocardiographic changes as an aid in the diagnosis of hypopotassemia or hyperpotassemia must take into account similar changes which may occur in other cardiac conditions.

We may briefly review the chief features necessary for making a diagnosis of potassium deficiency and for instituting potassium therapy. These are: (a), an awareness of the various conditions and diseases likely to be associated with this deficiency; (b), the presence of muscular weakness and paralysis, particularly those of the respiratory muscles; (c), characteristic electrocardiographic changes; (d), the concentration of the serum potassium.

*Treatment of Potassium Deficiency in Infantile Diarrhea.* As a consequence of Darrow's<sup>42</sup> demonstration that infantile diarrhea was characterized by a loss of intracellular potassium, and that this loss continued during the institution of the conventional saline-glucose therapy, he introduced a pro-

cedure which included the use of potassium chloride. Upon admission, the infant received an intravenous injection of whole blood or plasma (10 to 20 cc. per kg. of body weight); food and water by mouth was stopped. An intravenous infusion or subcutaneous injection of a potassium chloride-sodium lactate solution was then started. The composition of this solution, per liter, was as follows:  $K^+$ , 35 mM;  $Na^+$ , 122 mM;  $Cl^-$ , 104 mM; lactate, 53 mM. This mixture could be made conveniently by adding 2 gm. of KCl and 3 gm. NaCl to 250 cc. of M/6 sodium lactate and 500 cc. of water. A dose of 80 to 150 cc. of this solution per kg. of body weight was given during the first 24 hours. In addition, a 5% solution of glucose was given intravenously so as to make a total water intake of 150 to 280 cc. per kg. of body weight. After the first day, and as long as the stools remained watery, 20 to 50 cc. of the potassium chloride mixture were given per kg. of body weight and enough 5% glucose to make a total water intake of 150 to 200 cc. per kg. of body weight. Vitamin B complex and crude liver extract were also administered. Feeding was started and regulated in accordance with the progress of the patient.

It may be seen from the above that during the first day about 2.8 to 5.3 m.Eq. (about 0.2 to 0.4 gm. of KCl) were introduced per kg. of body weight. In his previous balance studies, Darrow<sup>18</sup> had observed that the average daily losses of potassium on the conventional glucose-saline therapy was about 1 to 1.5 m.Eq. per kg. In contrast, 2 infants who were placed on potassium therapy initially showed positive potassium balances of 3 and 8 m.Eq. per kg. of body weight during 4 days and 3.5 days of therapy. These results indicated intracellular deposition of potassium.

It may be readily appreciated that

Darrow's studies show a convincing biochemical and physiological justification for the use of potassium chloride therapy in infantile diarrhea. The question arises concerning the extent to which clinical results reflect this rational formulation. Prior to about 1920, it was generally thought that severe infantile diarrhea or, as it is also termed, intestinal intoxication, was a highly fatal condition with a mortality ranging from 80 to 90%. In 1926, Powers<sup>85</sup> reviewed 64 cases which had been treated in New Haven Hospital from 1922 to 1925. Nine had been admitted *in extremis* or had their treatment interrupted by being taken out of the hospital. Of 19 who received no systematic treatment, 14 (70%) died. Thirty-six patients were submitted to a systematic regime which consisted of: (a), withdrawal of all food by mouth; (b), blood transfusions; (c), administration of sodium bicarbonate; and (d), intraperitoneal, subcutaneous and intravenous injection of Ringer's solution. Feeding was initiated only when toxic symptoms had abated or disappeared, began with very small amounts and was increased gradually in accordance with the clinical status of the patient, until the total caloric requirement was reached in a week or 10 days. On this regime, 12 of the 36 patients (33%) died. In 1933, Karelitz and Schick<sup>54</sup> submitted a plan of treatment which stressed (a), a more radical and longer than usual rest for the gastrointestinal tract, and (b), the intravenous drip infusion of a glucose-saline or glucose-Ringer solution. The mortality in 53 cases treated by this method was 6 (12%). The average mortality for the preceding 10 years at the same hospital had been 64%. Campbell and Cunningham<sup>12</sup> reviewed 574 cases of non-specific infantile diarrhea. Parenteral fluid therapy consisted usually of subcutaneous administration of normal saline. In severely ill patients.

the fluids were also administered intravenously or intraperitoneally. Of the 574 cases, 283 were dehydrated upon admission; the mortality rate in these was 53.7%. In the 291 which were not dehydrated, the mortality rate was only 2.4%. The overall mortality rate was 27.7%. Smellie<sup>97</sup> studied 500 cases which had been admitted to the Birmingham Children's Hospital (England) for several years prior to 1939. The therapeutic regime consisted of subcutaneous injections of saline, intravenous injections of normal saline, glucose or blood, and withdrawal of food for the first 12 to 24 hours. The overall mortality was 240 (48%). However, when the whole group was subdivided into those who developed parenteral infection after admission to the hospital, those who had such infection at the time of admission, and those who never had any parenteral infection, the mortality rates were 78.8, 56.3 and 11.3%, respectively.

Much lower mortality rates have recently been reported. L. F. Meyer<sup>75</sup> has found that the use of sulfonamide drugs has decreased the mortality rate in Tel-Aviv from 50% before 1940 to 7% in recent years. During 1944 and 1945, Wehl, Rapoport and Dodd<sup>100</sup> treated 292 infants and children with acute diarrhea. The therapeutic regime consisted of continuous intravenous infusion of saline, glucose, plasma, blood, and sodium bicarbonate if the carbon-dioxide combining power was less than 30 vols. %. Sulfonamides were also administered and feedings were gradually initiated in accordance with the status of the patients. The patients' illness ranged from "mild" to "very severe"; about 40% fell into the group of "severely ill" and "very severely ill". Of the 292 patients, 22 (7.5%) died. Of these patients, 3 died within 3 hours after admission before adequate therapy had been instituted. Three other patients died of other causes after the

diarrhea subsided. If these 6 patients are excluded, the mortality was 16 of 286 patients (5.6%).

It is apparent from the considerations and the data which we have presented that, without considering for the moment the therapeutic use of potassium salts, the mortality rate in infantile diarrhea is dependent upon a number of factors. These are the state of dehydration and general condition of the infant upon admission, the presence, development and control of parenteral infection, the adequate parenteral administration of saline, glucose, blood, and lactate or bicarbonate and the judicious initiation and regulation of oral feeding. The available literature<sup>12,54,75,94,97,106</sup> indicates that the general rate of mortality may be about 20%, but that in certain hospitals, the rate may fall below 10%, and, as in the case of Wehl's report, as low as 5.6%.

In view of the considerations just presented, the therapeutic use of potassium chloride by Govan and Darrow<sup>42</sup> can now be evaluated more precisely. During the months of June, July and August, a control group of babies with diarrhea was treated at the Harriet Lane Home in Baltimore by the conventional methods. Only those babies were admitted who were severely ill and who, it was thought, would not recover unless they received hospital treatment. There were 59 babies in this control group but in 6 of these, death was associated with sepsis or prematurity; in this group there were 17 other deaths. The corrected mortality in this control group which did not receive potassium was 17 of 53 (32%). During the months of September to November, 52 cases received, as previously described, fluids and feedings containing potassium chloride. It was believed that the patients in this group had, in general, the same distribution of severity of ill-

ness as the control group. Of these 52 patients, there were 5 deaths. One death was associated with sepsis and another with prematurity. The corrected mortality was, therefore, 3 out of 50 (6%). On the basis that the control and potassium-treated groups were strictly comparable, the difference between the mortality rates of the 2 groups is highly significant and attests to the efficacy of the potassium therapy.

Butler and his associates<sup>11,90</sup> have recommended the therapeutic use of a solution which contains 2.24 gm. of sodium lactate, 0.58 gm. of sodium chloride, 0.89 gm. of potassium chloride and 0.25 gm. of potassium monohydrogen phosphate per liter of 10% dextrose. In terms of m.Eq. the concentrations per liter, are as follows: sodium, 30 m.Eq.; chloride, 22 m.Eq.; potassium, 15 m.Eq.; phosphate, 3 m.Eq. Forty infants with persistent infectious diarrhea were given about 150 to 200 cc. of this solution per kg. of body weight per day together with 50 to 100 cc. of saline; frequent transfusions of plasma and blood were also administered. None of these 40 infants died. It will be noted that the solution recommended by Butler was much more hypotonic with respect to sodium and chloride ions than that recommended by Darrow which contained 122 m.Eq. and 104 m.Eq. per liter of these 2 ions, respectively.

*Treatment of Potassium Deficiency in the Postacidotic Phase of Diabetes.* When Holler<sup>52</sup> surmised that the respiratory paralysis which he was observing in a diabetic during the postacidotic phase of treatment might be due to a potassium deficiency, he drew blood for determination of serum potassium, then injected 1.5 gm. of potassium chloride in a 2% solution during the course of 35 minutes. The serum before treatment was subsequently found to have a potassium con-

centration of 2.5 m.Eq. per liter. Within 20 minutes after the end of injection, the patient showed dramatic improvement, and her respirations became normal. Additional potassium chloride was administered subcutaneously and orally during the next 2 hours to prevent recurrence of respiratory distress; the total amount given was equivalent to 8.7 gm. of potassium chloride. The patient experienced no further difficulty during her stay in the hospital. Her serum potassium and her electrocardiographic pattern were restored to normal.

Although there have been no reports concerning potassium therapy in large groups of patients in the postacidotic phase of diabetes, there have appeared a number of case studies, similar to that reported by Holler<sup>52</sup>, which demonstrate rather convincingly that such therapy has been effective in counteracting the symptoms of potassium deficiency and averting the possibility of a fatal outcome. Such are the cases reported by Nicholson and Branning<sup>82</sup>, Frenkel and co-workers<sup>35</sup>, and Tuynman and Wilhelm<sup>104</sup>. Howard and Carey<sup>63</sup> have stated that potassium therapy in this condition is characterized, not only by the prevention of potassium deficiencies, but also by the absence of edema and hypoproteinemia and a quicker recovery to fitness and regulation by insulin.

The following doses and modes of administration have been found effective in relieving acute potassium deficiency of the postacidotic phase of diabetes: intravenous injection of 1.5 gm. of potassium chloride in a 2% solution during 35 minutes, followed by a subcutaneous infusion of a 200 cc. of a 2% solution of potassium chloride in 2 hours, and oral ingestion of 4 gm. of potassium citrate<sup>52</sup>; 0.6 gm. of potassium chloride by mouth every half hour until 3.6 gm. had been given<sup>82</sup>; 4 gm. of potassium chloride.



divided into 2 equal doses, by mouth<sup>55</sup>; 0.3 gm. potassium chloride by mouth at ½ hour intervals for 6 doses<sup>104</sup>.

We may see, then, that in general, between 2 and 4 gm. of potassium chloride have been found effective. This corresponds to between 30 to 60 m.Eq. of potassium. It will be recalled, however, that the loss of potassium during the development of diabetic acidosis and treatment by saline-glucose solutions may be as much as 300 to 400 m.Eq. It follows, then, that where the diabetic acidosis has been very severe or prolonged, as in Holler's case, larger doses, up to about 8 or 10 gm. (100 to 125 m.Eq.) of potassium chloride may be used during the first day of therapy, and may be continued if the symptoms of hypopotassemia do not abate. In administering such solutions parenterally it is necessary, in this as well as in other conditions, to regulate the rate of introduction so as to avoid toxic levels of potassium ion in the serum. Howard and Carey<sup>53</sup> suggest that the serum reaching the heart must not contain more than 7 m.Eq. potassium per liter. This will usually be accomplished if solutions containing between 40 to 90 m.Eq. (1 to 2 gm.) per liter are infused at rates ranging between 8 and 12 cc. (120 to 180 drops) per minute. The problem of potassium toxicity will be discussed more fully later.

*Treatment of Potassium Deficiency in Familial Periodic Paralysis.* We have seen that the hypopotassemia in this condition is not due to an intracellular potassium deficiency, but rather to some factor which causes a shift of potassium from the extracellular to the intracellular compartment. There have been no systematic studies to determine the minimal amount of potassium necessary to counteract the hypopotassemia. In general, substantial but non-toxic amounts of potassium chloride or citrate have been given and

found effective. Thus Herrington<sup>51</sup> treated 2 cases by administering orally 5 gm. of potassium citrate whenever prodromal symptoms of muscle weakness and soreness became evident. Pudenz and his associates<sup>86</sup> noted that the administration of 5 to 10 gm. of an aqueous solution of potassium chloride counteracted paralytic symptoms within 30 minutes to 1 hour and enabled the patient to walk 2 hours after administration. The concentration of serum potassium rose from 10 mg. to 24 mg. per 100 cc. (2.5 to 6 m.Eq. per liter).

Oral administration of 2 to 10 gm. of potassium chloride is adequate in most instances in abolishing episodes of paralysis and in preventing seizures<sup>69</sup>. However, there are some situations in which parenteral administration is necessary. For example, the patient reported by Pudenz and his associates<sup>86</sup> suffered a paralytic attack in which he became unconscious and required artificial respiration. The intravenous injection of 1 gm. of potassium chloride produced a striking improvement within 20 minutes; the patient sat up and was able to converse.

**POSTOPERATIVE POTASSIUM DEFICIENCY.** A number of observations have recently been made to the effect that hypopotassemia may develop postoperatively in patients who are given only saline, glucose and amino acids<sup>53,64,66,68</sup>. An idea of the therapeutic procedure in this condition may be gathered from the recent work of Howard and Carey<sup>53</sup>. A chronically ill patient was found, 17 days after operation, to be extremely asthenic, with shallow respirations and barely obtainable peripheral reflexes. The serum potassium was 1.8 m.Eq. per liter. Amounts of potassium ranging from 54 to 134 m.Eq. (4 to 10 gm. of potassium chloride) per day were given for the next 8 days. The concentration of potassium in the serum rose slowly

until it attained a value of 3.2 m.Eq. per liter on the seventh day of therapy when there was a dramatic improvement in the clinical condition of the patient; he felt stronger, appeared more alert and the reflexes were now readily elicited. Two days later the serum potassium had risen to 4.1 m.Eq. per liter and the electrolyte pattern of the serum had been restored to normal. In this case a total of 991 m.Eq. of potassium (75 gm. of potassium chloride) had been administered.

**POTASSIUM TOXICITY.** A knowledge of the circumstances under which potassium may become toxic is necessary in order to withhold its administration when contraindicated or to avoid overdosage when such administration may ordinarily be employed. The reader will recall the electrocardiographic results which Winkler, Hoff and Smith<sup>110</sup> obtained upon infusion of isotonic (1.12%) potassium chloride into dogs. Cardiac arrest and death occurred at a serum potassium concentration of 14 to 16 m.Eq. per liter. This range of concentrations was obtained when the solution of potassium chloride was infused at a rate of 0.4—0.8 cc. per min. per kg. for about 40 minutes and when a total of 0.2 to 0.3 gm. of KCl (3 to 4 m.Eq.) per kg. had been given. A much smaller amount, 0.05 gm. or 0.7 m.Eq. per kg. produces death if it is introduced rapidly enough so that a serum concentration of about 15 m.Eq. per liter is produced. On the other hand, Winkler and Smith<sup>112</sup> showed that when doses of 0.2 to 0.3 gm. (3 to 4 m.Eq.) of potassium chloride were infused into dogs at a sufficiently slow rate, the concentration of potassium in the serum rose only about 2 to 3 m.Eq. and no grave symptoms ensued. Calculation from this rise and the excretion of potassium indicated that considerable amounts had been deposited intracellularly.

It would appear from these experi-

ments that the determining factor in toxicity and death as a result of administration of potassium salts is the concentration of potassium ion in the plasma and extracellular fluid. A rapid injection of a small amount can prove fatal whereas a slow injection or the ingestion of a large amount can be innocuous. The question arises whether these relationships also obtain in man.

Large amounts of potassium salts can be taken by mouth with the production of only minor toxic symptoms. Talbott and Schwab<sup>100</sup> record the ingestion of 30 to 36 gm. of potassium chloride daily in 3 equal doses without any apparent ill-effects. Keith and his co-workers<sup>58,59,60</sup> showed that the ingestion of potassium chloride or bicarbonate by normal individuals in doses ranging from 9.5 to 17.5 gm. (126 to 172 m.Eq.) led to paresthesias of the hands and feet, and increases in the amplitude of the T wave. The concentration of potassium in the serum rose from a normal value of about 16 to 20 mg. per 100 cc. to a level of about 30 mg. per 100 cc. or 7.5 m.Eq. per liter. The ingestion of smaller doses, 5 gm. of potassium bicarbonate (50 m.Eq.) by normal individuals, did not lead to any paresthesias, to only slightly detectible changes in the electrocardiogram and to only small increases in the concentrations of potassium. The increases were about 2 to 4 mg. per 100 cc. or 0.5 to 1.0 m.Eq. per liter.

It has already been pointed out that on the basis of experimental work in dogs, the lethality of potassium appears to be dependent on the concentration of the serum potassium; this fatal level in normal dogs is about 15 m.Eq. per liter or 60 mg. per 100 cc. It is obviously difficult to obtain comparable data in normal man. In the course of treating an infant with diarrhea by the subcutaneous in-

jection of a solution containing potassium chloride, Govan and Weiseth<sup>43</sup> observed the development of potassium toxicity. The infant survived although a level of 12.3 m.Eq. per liter (49 mg. per 100 cc.) of potassium was attained. Howard and Carey<sup>53</sup> record an experience in which a considerable amount of a solution of potassium salt was injected within a few minutes into a patient who clearly had hypopotassemia. Although no determination for serum potassium was done, the cardioscope showed an abrupt change from a low to a high potassium pattern. The patient died before the injection could be stopped. This case illustrates the necessity for introducing potassium salts parenterally at such a rate as not to exceed a concentration in the serum which is toxic to the heart.

It has been possible to obtain a more precise idea of the toxicity of potassium in patients with renal impairment. The following data show that the lethal level of serum potassium in such patients is about 10 m.Eq. per liter. Marchand and Finch<sup>71</sup> reported 2 cases of spontaneous potassium intoxication in patients with uremia; no potassium other than that in the food or in blood transfusions had been given. It was possible to follow the electrocardiographic changes and the concentrations of potassium in the period immediately preceding death. In one patient in whom the N.P.N. had ranged from 155 to 208 mg. per 100 cc., the concentration of potassium was 9.2 m.Eq per liter 20 minutes before death and 9.8 mEq. per liter in blood taken from the heart immediately after death. In a second patient with an N.P.N. of 258 mg. per 100 cc., the concentration of potassium was 9.2 m.Eq. per liter 3 and  $\frac{1}{2}$  hours before death and 10.1 m.Eq. at death. Stewart, Shephard and Horger<sup>98</sup> also reported an instance of spontaneous

development of potassium intoxication and death in the course of the nephrotic stage of subacute glomerulonephritis; the concentration of potassium was 10.6 m.Eq. per liter at the time that the electrocardiogram showed auricular standstill and intraventricular block. It will be shown presently that in some studies in which potassium salts were fed to patients with renal impairment, serum potassium levels approaching those just recorded were obtained without the accompanying development of grave toxicity.

It may be of interest at this point to describe the clinical symptoms of hyperpotassemia and potassium toxicity. We have already noted the cardiac findings, particularly as evidenced in the electrocardiogram. Keith and his co-workers<sup>59</sup> observed that paresthesias of the extremities developed when the concentration of the potassium in the serum approximated 7.5 m.Eq. per liter. This held for normal individuals as well as those with renal insufficiency. Finch, Sawyer and Flynn<sup>30</sup> found that flaccid paralysis may also be present at higher, near-lethal levels of potassium in the serum. Such paralysis may involve the extremities and, to a lesser degree, the trunk.

The susceptibility of patients with renal impairment to hyperpotassemia and potassium toxicity is, quite obviously, due to decreased excretion of potassium. However, such patients may have a tissue potassium deficiency. It is of considerable importance from a therapeutic point of view, to know to what extent they may receive potassium. Greene and his associates<sup>15</sup> found that the ingestion of 19 mg. of potassium chloride (0.26 m.Eq.) per lb. of body weight by a patient with chronic glomerular nephritis increased the concentration of serum potassium to 44 mg. per 100 cc. (11 m.Eq. per liter); no statement was made concerning the development of toxicity.

This observation is not in agreement with those of Marchand and Finch<sup>71</sup> and of Stewart, Shepard and Horger<sup>98</sup> which indicate that 10 m.Eq. per liter is a lethal level. Winkler and his co-workers<sup>111</sup> administered oral doses of potassium ranging from 67 to 134 m.Eq. (5 to 10 gm. of KCl) to 5 patients with renal impairment. The concentrations of serum potassium increased in each of these patients; the maximal levels ranged from 6.3 to 8.0 m.Eq. per liter. Although similar doses did not produce any higher levels of serum potassium in normal individuals, the decrease to pre-ingestion levels was much more delayed in the nephritic than in the normal. No symptoms of toxicity attributable to potassium were observed by Winkler and his associates in the patients with renal impairment.

Keith and Osterberg<sup>59</sup> have, however, obtained some toxic effects with somewhat smaller doses of orally administered potassium. Ten patients with severe renal insufficiency received 5 gm. of potassium bicarbonate (50 m.Eq. of potassium). One of these patients had a blood urea of 74 mg. per 100 cc. In 9 of these patients, the concentrations of potassium before ingestion of potassium bicarbonate ranged from 21.9 to 28.4 mg. per 100 cc. (5.6 to 7.3 m.Eq. per liter). One and a half hours after ingestion, the concentrations in these patients had increased in each case and ranged from 23.1 to 37.1 mg. per 100 cc. (6.0 to 9.5 m.Eq. per liter). Paresthesias of the extremities occurred in 4 of the patients; the serum potassium in these instances ranged from 31.1 to 35.8 mg. per 100 cc. (8.0 to 9.2 m.Eq. per liter). In the 6 patients in whom paresthesias did not develop, the serum potassium ingestion ranged from 19.9 to 37.1 mg. per 100 cc. (5.1 to 9.5 m.Eq. per liter). Electrocardiographic studies of these patients showed a definite toxic effect on the heart, namely, intraventricular

block, in only 1 case; the concentration of serum potassium in this patient was 37.1 mg. per 100 cc. (9.5 m.Eq. per liter).

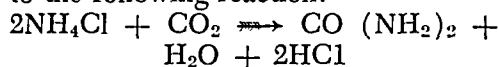
The studies which we have reviewed would indicate that the administration of potassium to patients with renal insufficiency should be a very guarded procedure. Although potassium intoxication may occur spontaneously, the work of Keith and Osterberg<sup>59,60</sup>, of Greene<sup>45</sup>, and of Winkler<sup>111</sup> indicates that small amounts of potassium, about 50 m.Eq. (3.7 gm. of KCl) may be given by mouth without serious danger to some patients with renal insufficiency. Although, therefore, the administration of potassium with renal damage is in general contraindicated, it would seem that when there is real evidence of potassium deficiency in such a patient, the cautious administration, under proper clinical supervision and with proper laboratory guides, of small amounts of potassium by mouth is to be considered. Even the intravenous infusion at very slow rates is not out of the question. However, this field of therapy will be greatly aided by further investigations concerning the tolerance to, and cellular storage of potassium in patients with renal insufficiency.

**Ammonium Chloride.** Ammonium chloride has a number of therapeutic uses. It is, however, with its application in the treatment of alkalosis that we are here particularly concerned.

**ACIDIFYING ACTION OF AMMONIUM CHLORIDE.** The production of acidosis in man by ammonium chloride was first demonstrated by Haldane<sup>47</sup>. After ingesting amounts ranging from 5 to 55 gm., either in one or several doses, Haldane observed that this compound decreased the alveolar carbon dioxide pressure and the carbon dioxide capacity of the blood. Respiration increased in depth and frequency and, in one experiment, the volume breathed per

minute at rest increased 70%. Simultaneously, the urinary excretion of titratable acid and ammonia rose. Haldane assumed, although he did not demonstrate, that the formation of urea was increased. This, however, has been observed by subsequent investigators. The acidifying action of ammonium chloride has been confirmed by many investigators and the mechanisms of the body's reaction to the ingestion of this compound and other acid substances has been studied in great detail<sup>31,36,39,56,63,69,93</sup>.

Haldane postulated that the ammonium chloride was metabolized to urea and hydrochloric acid according to the following reaction:



This may be regarded as an overall reaction. It has been established that the liver is the physiologically important site of the conversion of ammonia into urea<sup>84</sup>. The way in which ammonia is incorporated in the course of metabolic processes to form arginine, the immediate precursor of urea, has been considered in great detail by Krebs and Henseleit<sup>62</sup>, Cohen and Hayano<sup>14</sup>, Borsook and Dubnoff<sup>6</sup>, and, most recently by Ratner and Pappas<sup>60</sup>. It may be expected that parenterally administered ammonium chloride will have essentially the same metabolic fate. In the course of a study of the intravenous injection of hypertonic solutions of various chlorides, Whelan<sup>107</sup> found that 0.1 gm. ammonium chloride per kg. of body weight could be injected per minute without toxic effect. This dose caused a decrease in the pH of the urine and an increase in the excretion of urea.

The effect of the introduction of ammonium chloride into the body on the acid-base regulating mechanisms may be described briefly. The alveolar ventilation is increased and, accordingly, the alveolar carbon dioxide pres-

sure is decreased. For example, in a subject studied by Sartorius, Roemmelt and Pitts<sup>93</sup>, the alveolar pressure decreased from a normal level of 41.0 mm. Hg. to one of 23.9 mm. after the ingestion of 40 gm. of ammonium chloride over a period of 3 days. This was indicative of an increase of 70% in alveolar ventilation. Gamble and his co-workers<sup>37,39</sup> showed that, in response to continued administration of ammonium chloride, there is first an increase in titratable acid and fixed base but that later, ammonia is substituted in progressively increasing amounts for fixed base in the urine. Pitts and his associates<sup>93</sup> have recently studied the relationship of electrolyte pattern to renal function in ammonium chloride acidosis produced by feeding 10 to 15 gm. over a period of several days. They observed that the plasma bicarbonate fell in exact proportion to the increase in plasma chloride. Since the load of bicarbonate presented to the tubules was decreased, the reabsorption of chloride increased. However, this increase was not large enough to prevent a net loss of chloride in the urine. Early in acidosis, the excess urinary chloride was neutralized mostly by sodium from the body buffers. The loss of sodium was reflected in a decrease of the concentration of sodium in the plasma. The loss of water from the body was derived chiefly from the extracellular fluid compartment. Of particular interest were the findings obtained within 2 hours after the ingestion of 10 gm. of ammonium chloride. The excretion of ammonia, as well as that of titratable acid, increased.

*Treatment of Alkalosis.* Bothe<sup>7</sup> appears to have been the first to use ammonium chloride by mouth in the treatment of alkalosis occurring either preoperatively or postoperatively. However, no specific doses were mentioned. Chalmers<sup>13</sup> treated 2 cases of alkalosis due to severe intestinal

obstruction from abdominal tuberculosis by administering per rectum 12 gm. of ammonium chloride dissolved in 5 to 6 ounces of water.

The use of parenteral ammonium chloride therapy for treatment of alkalosis was initiated by Zintel, Rhoads and Ravdin<sup>113</sup>. They found that the decrease in the serum carbon dioxide in a 150 lb. adult ranged from 0.6 to 1.5 and averaged 1.1 vols. % per gm. of ammonium chloride injected intravenously. Accordingly, they recommended a dose of 16 mg. per kg. of body weight in order to reduce the serum carbon dioxide content by 1 vol. %. Two % solutions of ammonium chloride in water, glucose or saline were employed. For example, in one patient with chronic peptic ulcer and stenosis, the infusion of 700 cc. of a 2% solution decreased the carbon dioxide content from 113 to 85 vols. %.

The effect of parenteral administration of ammonium chloride in the treatment of alkalosis of congenital hypertrophic pyloric stenosis in infants has been demonstrated by Forbes and Erganian<sup>33</sup>. The previous treatment of this condition consisted in parenteral administration of dextrose and saline or lactate-Ringer. It was thought that if sufficient water and electrolyte were given, a satisfactory correction of the alkalosis would be attained through renal activity. However, such an adjustment usually required 1 to 2 days and might not be accomplished in cases of very severe alkalosis. Indeed Forbes and Erganian refer to the occurrence of death in several infants before they could be prepared for operation.

Restoration toward a normal electrolyte pattern and acid-base equilibrium was achieved much more rapidly by the intravenous infusion of a 1/6th molar solution of ammonium chloride (8.9 gm. per liter) in isotonic saline or Ringer's solution. The doses ranged from 10 to 37 cc. per kg. of body

weight and were administered during the course of 30 minutes. Maximal decreases in the carbon dioxide content and pH, and the maximal rise in the concentration of chloride were attained within 1 to 3 hours after the end of the infusion. For example, a severely alkalotic infant weighing 2.2 kg. was given 60 cc. of the ammonium chloride solution. The CO<sub>2</sub> content decreased from an initial value of about 105 vols. % to about 68 vols. % at the end of 2 hours. The pH fell from 7.63 to 7.47 and the chloride increased from 73 to 94 m. Eq. per liter.

The extent to which the normal electrolyte pattern and the acid-base balance is restored depends on the severity of the initial alkalosis and the dose of ammonium chloride. However, only a very general rule can be given concerning the relationship between the two. Upon theoretical grounds, it may be calculated that 1 cc. of a 1/6th molar solution of ammonium chloride should neutralize an equivalent amount of bicarbonate and reduce the carbon dioxide content by 22.4/6, or 3.7 cc. per liter of serum. If it is assumed that ammonium chloride and the bicarbonate are distributed in the total body water, then 1 cc. of ammonium chloride solution per kg. of body weight should reduce the carbon dioxide content by  $3.7 \times 3/2$  or 5.6 cc. CO<sub>2</sub> per liter of serum or 0.56 vols. %. Actually, in the series studied by Forbes and Erganian, the lowering of the serum carbon dioxide content ranged from 0.33 to 1.77 and averaged 0.88 vols. % for every cc. of molar-sixth ammonium chloride solution administered per kg. of body weight. The cause for this variability requires further investigation.

Grace and Barr<sup>14</sup> studied a series of patients with intestinal obstruction in whom alkalosis had been precipitated by a combination of frequent gastric lavage and the administration of large

amounts of sodium lactate in conjunction with the use of sulfadiazine. Acute delirium was present in most of these cases. It was found that the intravenous infusion of a liter of a 2% solution of ammonium chloride during a period of 2½ to 3 hours resulted in an immediate improvement of the patient and elimination of the disturbing symptoms.

**TOXIC EFFECTS OF AMMONIUM CHLORIDE ADMINISTRATION.** Rizvi and Lucknow<sup>92</sup> used rapid injections of 10 cc. of a 5% solution of ammonium chloride to produce convulsion in schizophrenic patients. Such administrations correspond to a dose of about 7 mg. per kg. This dose is much less than the total doses, 89 to 330 mg. per kg., employed by Forbes and Erganian. However, these latter doses were usually infused very slowly during 30 minutes. Indeed, in one case, when a dose of 30 cc. per kg. of 1/6th molar ammonium chloride was given in 18 minutes, an interval shorter than the usual 30 minutes,

toxic symptoms developed; the baby became pale, had twitchings of the eyelids and hands, breathed irregularly, developed bradycardia and showed a poor response to painful stimuli. It would, therefore, appear that the rate at which ammonium chloride is administered must be watched carefully in order to avoid toxic reactions.

In conclusion, it may be noted that potassium salts and ammonium chloride have gained an important place during the past few years in the armamentarium of parenteral fluid therapy. The judicious use of these substances has in many instances ameliorated the condition of the patient or even proven a life-saving measure. Basic studies of electrolyte and water balance and of renal function have done much to supply a rational basis for the use of these substances, but further investigations of this kind are indicated to increase and broaden their therapeutic effectiveness.

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# RADIOLOGY

UNDER THE CHARGE OF

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## ELECTROKYMOGRAPHY

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IN the application of roentgen methods to the investigation of clinical problems, radiologists and their colleagues have been principally concerned with the development of procedures which demonstrate changes in anatomical structure. Relatively few efforts have been directed toward the development of methods which detect physiologic disturbance. It is perhaps not surprising that radiology has followed this pattern in its early stages of growth. The evolution of roentgen engineering has been such that radiologists have been largely limited to methods in which one or more independently exposed films are made of the structure under examination. Although by proper timing of these exposures an evaluation of some functional processes may be attempted, such methods patently favor the visualization of anatomical structure rather than physiologic pattern.

Over the past few years, a number of developments have occurred which may well alter the trend which has

heretofore existed. New techniques in angiocardiology have opened the door to the study of many problems in cardiovascular physiology. The recent application of Schmidt optics to the field of photofluorography may soon make possible motion pictures of a quality that compares favorably with conventional roentgenograms. Also, the roentgenoscope, which inherently would be an excellent physiologic tool if it were not for its poor rendition of detail, may soon have its deficiencies corrected if current research to intensify or brighten the fluoroscopic screen is successful.

In addition to the foregoing there has been one other instrumental development which appears to have considerable potential value in the study of physiologic phenomena. This is the electrokymograph<sup>15</sup>, a device primarily developed for the recording of cardiac motion, but an instrument that may also be used to study the motion of any structure that can be seen roentgenoscopically or to study minute

changes in tissue density which may occur from physiologic activity.

The electrokymograph fundamentally consists of a small roentgen radiation detector, a simple amplifier, an oscillograph and a well regulated power supply. The radiation detector consists of a multiplier phototube and a small fluorescent screen, placed directly over the phototube's sensitive surface. The detector is attached to the frame of a conventional roentgenoscope and is mounted so that it assumes a position between the patient and the roentgenoscopic screen.

In the recording of cardiac motion with the instrument, the radiation detector is first centered roentgenoscopically over the border of the cardiac silhouette and then with the roentgen beam still turned on, the recording oscillograph is set in motion. As the cardiac border moves to and fro, the heart shadow may be seen to cover an increasing amount of the detector's fluorescent screen during the expansile phase of the cardiac cycle and a decreasing amount of the screen during the contractile phase. The intensity or brightness of the Roentgen rays passing through the detector's fluorescent screen thus varies in accordance with the motion of the heart border. Now these rays cause the emission of fluorescent light from the screen in proportion to their intensity and the underlying phototube reacts to this light by generating an electric current in proportion to the intensity or brightness of the fluorescent light. Therefore, the recording oscillograph to which the phototube is connected prints a wave whose amplitude is a function of the motion of the cardiac border under study.

In their original work with the electrokymograph, Henny and Boone<sup>15,16</sup> thought it important that the instrument's radiation detector be always centered with its long axis

parallel to the structural motion being recorded. Subsequent experimental and theoretical investigations have proven this restriction to be unnecessary, however, and accordingly the mechanical design of the instrument has been simplified.

It may be of interest to the reader at this time to relate a few of the events that led to the early research in electrokymography. Jacobi, Janker and Schmitz<sup>20</sup> had conceived the idea of using an electronic radiation detector to record cardiac motion during the early 1930s. At that time the only roentgen device with which cardiac motion might be recorded was the roentgen kymograph, an instrument first proposed by Sabat<sup>31</sup> and later perfected by Stumpf<sup>38</sup>. This device, then as now, consisted of a lead diaphragm in which was cut a series of narrow transverse slits approximately one half inch apart. This diaphragm was placed in front of a roentgenographic film and during the exposure of a patient's chest, the film moved slowly downward behind the diaphragm. Any motion of the structures in the chest was recorded therefore on the film. Although much good work has been accomplished by this device<sup>1,12,17,18, 21,32,33,34,35</sup>, the analytic difficulties inherent in the unsharpness, the smallness and the brevity of its recorded waves have prevented it from becoming a widely used tool either in general radiology or in the study of physiologic processes.

As a means of overcoming the limitations of the roentgen kymograph, first Jacobi and his co-workers<sup>20</sup> and later Heckmann<sup>14</sup> considered the development of an instrument in which an ionization chamber served as a radiation detector. Unfortunately, within the limits of practical design it was not possible to build an instrument of this type which was both stable in operation and faithful in its recording char-

acteristics. Accordingly their efforts were not too successful. Early in 1940 however, the present writer<sup>29</sup> had begun to use multiplier phototubes in Roentgen-ray exposure control apparatus and it appeared that the characteristics of this device were such that it might serve as an excellent radiation detector for recording cardiac motion. The pressure of war activity prevented anyone from taking advantage of this development until arrangements were made with the U. S. Public Health Service early in 1945 to have Boone assigned to the laboratory of Chamberlain and Henny. Boone went to Philadelphia and work on the electrokymographic project was begun.

When the first instrument was constructed, there immediately arose the question concerning what name should be applied to the device. In correspondence and conference between Henny, Boone, Chamberlain and the author, several names were proposed including the term, fluorocardiograph. This name was discarded since the instrument was potentially useful in other fields than cardiography. The author suggested the term, electrokymograph, and although this name had several shortcomings, it was finally adopted by the group. Possibly the term, fluorokymograph, would have been better. However, the instrument has found use as a plethysmograph<sup>9</sup> in which visible light instead of roentgen radiation is used as the activating medium. In view of these and other considerations the name, electrokymograph, has persisted.

In addition to the pioneer work by Henny and Boone, fundamental electrokymographic research has more recently been conducted by Hjelmare<sup>10</sup> in Sweden and Marchal<sup>28</sup> and Lian and Minot<sup>23</sup> in France. Hjelmare employs a Geiger-Muller counter as his radiation detector, whereas the French workers use conventional phototubes

and sensitive amplifiers. Both groups have obtained good results. The simplicity of the multiplier phototubes employed by American investigators, however, favors the use of these devices over their European counterparts.

In their early work with the electrokymograph, Boone, Henny and their co-workers<sup>2,3</sup> devoted most of their effort to the analysis of cardiac motion and in particular to the motion of the left ventricle, the right auricle, the aorta and the pulmonary artery. For each of these structures they obtained complex, yet rather characteristic wave patterns. In order to correlate these wave phenomena with the events in the cardiac cycle that were responsible for them, it was necessary to record simultaneously with the electrokymographic tracings, a reference tracing of some other cardiac activity whose wave patterns were well understood. The carotid sphygmogram was used for this purpose.

Electrokymographic tracings were made by: 1, placing the patient in front of a roentgenoscope to which the instrument's radiation detector was attached. 2, guiding the radiation detector under roentgenoscopic control to a position over the heart border and, 3, then setting the oscillograph in motion. During the recording of the cardiac activity, the patient was requested to stop breathing.

The patients were examined in both the upright and recumbent positions. The sensitivity of the electrokymograph was adjusted individually for each patient so as to yield a tracing in which the amplitude of the waves approached 15 to 20 mm. With such an amplitude, the resolution of the various complex patterns was excellent and permitted ready analysis.

In this experimental work, the electrokymograph was arranged so that upward moving limbs of the recordings represented expansile or filling

phenomena of the heart while downward moving limbs represented contractile or emptying phenomena. The steeper the slope of a wave limb, the more rapid was the action or movement, and the less steep the slope, the slower was the action. Changes of slope upon a limb, in general, represented changes in speed of action and notches or serrations in the wave pattern represented smaller superimposed changes of action.

The wave forms for each of the 4 border areas of the heart and great vessels under investigation were found to be quite characteristic and to resemble closely the respective volumetric wave forms that are well known to physiologists. In spite of this basic resemblance to volumetric curves, however, certain differences were noted. It is believed that these differences are caused by factors which may be called "positional" in nature.

During ventricular systole and diastole, the heart undergoes a general movement because of its structure and relationship to the great vessels. Early in systole the long axis of the heart shortens as the base and apex move toward one another. At the same time the broad axis widens and the shape of the heart changes from an ellipsoidal to a globular configuration. This action frequently produces small outward movements of portions of the ventricular wall in early systole instead of the expected inward movement that would ordinarily occur when the volume of the heart is decreasing. In addition to the foregoing, 2 other positional changes have been described. One is caused by the pendulum motion which occurs when the aorta straightens; the second is a rotational motion which is caused by the spiral arrangement of the ventricular muscle bundles. During systole, this rotation causes cranial displacement of the apex, while in diastole the motion is reversed. These positional

changes are of course superimposed on the volumetric changes and hence create a wave pattern of increased complexity. Sometimes they may be opposite in direction to the volumetric displacement and thus tend to counteract it; at other times they may be in phase with it and thereby produce an additive effect. It has been observed that these positional factors exert their influence principally during the early stages of systole and diastole.

The electrokymographic tracing of the left ventricular border has 2 major components, one descending, the other ascending. Each is preceded by a serration of variable amplitude and direction. The beginning of the serration that precedes the descending ejection phase of the cardiac cycle marks the onset of ventricular contraction and the raising of the intraventricular pressure to a sufficient level to close the mitral valve. As the contraction of the ventricular fibers continues the intraventricular pressure rises still further until the aortic valve opens. The time interval between the closure of the mitral valve and the opening of the aortic valve is called the isometric contraction phase of the heart cycle. Since there are no significant volumetric changes of the heart during this phase, the wave form of the electrokymographic tracing is entirely the result of positional changes of the heart. Also since the character of these positional changes varies widely from individual to individual and also from one region of the ventricle to another in the same individual, the wave form is quite variable. Usually however, the curve appears as a minor descending limb of gentle slope lasting for approximately 0.06 second.

When the aortic valve opens, blood is ejected rapidly into the aorta. During the early period ejection, positional factors of the heart continue to play a prominent role in determining the

ventricular wave form of the electrokymographic tracing. Frequently the ventricular wall exhibits a brief outward motion before its major inward motion occurs and hence the tracing may present a minor ascending limb of gentle upward slope before the major descending limb of ventricular ejection takes place. Toward the end of the ejection phase, the flow of blood into the aorta slows because of pressure equalization and the steep descending limb of the electrokymogram frequently tapers off.

At the end of ventricular systolic ejection, the phase of protodiastole, the first stage of diastole, occurs. This phase takes place just before the closure of the aortic valve and is usually marked on the electrokymogram by a minor upward serration, approximately 0.04 second in duration. However, as this wave form is principally the result of positional changes in the heart, it therefore varies from one individual to another to a considerable degree.

When the aortic valve closes, there follows a short interval before the mitral valve opens, called the isometric relaxation phase of the cardiac cycle. During this phase the ventricle is a closed chamber and therefore undergoes no volumetric change. Therefore here again, positional changes of the heart are the cause of any movement of the cardiac border. Usually this phase is marked on the tracing by a minor downward serration, approximately 0.10 second in length.

When the mitral valve opens there is an initial inrush of blood which carries the ventricular wall outward. This event is recorded electrokymographically as a major ascending limb of steep slope. This portion of the tracing marks what has been called the rapid diastolic filling phase of the cardiac cycle. It is followed by a phase in which the filling of the ventricle takes place at a slower rate and during which

the electrokymogram continues to ascend but at a somewhat diminished slope. This phase, called the slowed diastolic filling phase, leads directly into the isometric contraction phase to begin again the cardiac cycle.

It will be evident from the foregoing that electrokymograms of the left ventricle constitute a powerful method for recording the mechanical events that take place within the heart. Electrograms of the pulmonary artery and the aorta also reveal with striking definition the phenomena associated with those structures. The electrokymogram of the pulmonary artery presents a wave form with a sharply rising limb, a rounded crest and a slowly descending limb. The sharply ascending limb marks the vigorous ejection phase of ventricular systole and begins at the opening of the pulmonary valve. The first part of the descending limb probably occurs during the late phase of ventricular systole. Some distance from the peak of this limb there is a brief notch which is related to the closure of the pulmonary valves.

The electrokymogram of the aorta is similar in many respects to that of the pulmonary artery. It frequently is asynchronous with the tracing of the pulmonary artery, however, and therefore may be differentiated from it. Its incisural notch also is very much less prominent than that of the pulmonary artery.

A truly characteristic electrokymogram for the right auricle has been extremely difficult to establish. This appears to be due to the fact that the right ventricle usually superimposes its motion upon it and thereby creates a wave pattern that is difficult to analyse. However, it has been found that with careful time measurements and cross correlations, the time of auricular systole can usually be identified. The lower the point chosen on the right

auricular border, the more prominent is the influence of the right ventricle and the greater is the difficulty in defining the auricular activity. Indeed in many cases that have been studied, a pure ventricular wave has been recorded on the heart border in the vicinity of the cardio-hepatic angle. Thus the right ventricle may frequently contribute to the right heart border in the antero-posterior silhouette.

Until now, our discussion has been concerned mainly with the application of electrokymography to the study of normal physiologic phenomena in the heart and great vessels. A review of the literature pertaining to its use in abnormal physiologic states therefore appears to be in order. However, before proceeding to this phase of the subject, it is worthwhile to direct attention first to a number of engineering problems that have been encountered in electrokymographic development. In general, these problems have had a somewhat limiting influence on the breadth of application of the instrument.

As we have seen, the wave forms presented in electrokymograms of the heart are quite complex. The faithfulness with which the tracings actually record cardiac movement therefore is dependent on the frequency response of the electrokymograph. If the instrument is able to record equally well all of the frequencies generated by the cardiac segment under investigation, then the tracing will constitute a precise record of cardiac motion. On the other hand, if one of the movements of the heart generates a wave form of let us say 20 cycles per second and the electrokymograph has a frequency response that extends only from 0 to 10 cycles per second, that particular movement of the heart will go unrecorded; hence the electrokymogram will not constitute a faithful record of the cardiac phenomena.

Now electrokymographs using multiplier phototubes and calcium tungstate fluorescent screens as their radiation detectors inherently are limited in their frequency response only by the design of their amplifier and oscillographic equipment. Indeed, if necessary, these components can easily be designed to provide a frequency response from 0 to several kilocycles. However, the characteristic of present-day roentgenoscopes make the use of such equipment quite impossible. Conventional roentgenoscopes are operated with raw AC or unfiltered rectified AC potentials and hence the intensity of the Roentgen rays generated by them rises and falls periodically at a frequency of 60 or 120 cycles per second. If means are not provided in the electrokymograph to attenuate sharply these frequencies, the tracings that result are essentially unreadable. Now, it is not possible to attenuate a particular frequency without causing some attenuation of frequencies in the nearby ranges. In fact, unless considerable care is taken, the frequency response of an electrokymograph which contains provision for filtering out the 60 or 120 cycle signal arising in the roentgenoscope, may also discriminate severely against frequencies as low as 2 or 3 cycles. Kay, Wood, Zinsser and Benjamin<sup>22</sup> measured the frequency response of one electrokymograph and found the response at 5 cycles per second 39% lower than at 1 cycle per second; at 20 cycles the response was down 87%. It is quite obvious that such an electrokymograph will be unable to record much of the finer detail that may exist in a cardiac activity.

Although the first electrokymographs exhibited poor frequency responses, it is fortunately possible to design instruments that have a flat response from zero to about 30 cycles and still effectively filter out the 60 or 120 cycle signal from the roentgenoscope. Hence-

forth, electrokymographs having such characteristics should be easily attainable and it will be interesting to follow the additional information that these instruments will provide. It may be worthwhile to explore the possibilities of an electrokymograph operated from a constant potential roentgenoscope. If the instrument is able to record over a truly wide frequency range, the resulting high resolution of the device may provide information far beyond our present limits.

Another engineering problem that has been encountered in electrokymography is the difficulty with which the amplitude of the recorded tracing can be correlated with the amplitude of the actual motion under investigation. When a thin patient is examined, the intensity of the roentgen radiation reaching the electrokymograph is high and hence a normal cardiac excursion will produce an abnormally large amplitude in the electrokymogram. Conversely when the patient is overweight the intensity of the roentgen radiation incident upon the electrokymograph will be low; under these conditions the same amount of cardiac motion will produce a tracing of low amplitude. This difficulty may be overcome to some extent by an adjustment of the sensitivity of the electrokymograph to meet the changing intensity of the radiation that exists from one patient to another. Unfortunately, however, it is extremely difficult to calibrate such a sensitivity control in a manner that will insure a quantitative relationship between the amplitude of the electrokymogram and the amplitude of the motion that produced it. On the surface the underlying causes of this difficulty may not be readily apparent. However, it must be remembered that the electrokymograph is an instrument that records changes in light intensity received from a Roentgen-ray fluorescent screen. A moving struc-

ture, such as the heart or one of the great vessels, therefore will generate a wave pattern on the instrument's oscillograph.

Now the heart and great vessels differ widely in their ability to absorb roentgen radiation. The heart, being a large structure, absorbs a large percentage of the radiation projected through it while the pulmonary artery, being of much smaller caliber, absorbs only a small percentage of the radiation incident upon it. Accordingly, a given movement of the heart will produce tracings of much greater amplitude than the same amount of motion in the pulmonary artery. This same phenomenon will also cause the production of electrokymograms of different amplitude in 2 patients with equal average Roentgen-ray transmission and equal cardiac motion, if in 1 patient, the heart is larger than in the other.

From the foregoing it appears that the solution to the problem of correlating movement amplitude with tracing amplitude is well nigh insurmountable. With this thought in mind, a number of workers have expressed the opinion that this problem in reality is of no great importance under most circumstances. They point out that the great amount of information provided by the high resolution of electrokymographic tracings permits one to resolve most problems to which the instrument is applied. They further state that if quantitative information on the amplitude of a given motion is desired, it may be easily obtained from a roentgen kymographic film. Although this reasoning is doubtless sound, it is hoped that efforts will be continued to find ways and means of solving the problem.

During the past few years, electrokymography has been used by an increasing number of workers in the study of normal and abnormal cardiac physiology. Characteristic patterns



have been established for myocardial infarction and aneurysm, constrictive pericarditis, tricuspid and mitral heart disease and a number of congenital anomalies. Chamberlain<sup>6</sup> first demonstrated the spectacular changes that occur in the ventricular electrokymogram taken in the region of a myocardial infarct. In this situation the major descending and ascending limbs of the tracing that normally occur during the ejection and diastolic filling phases are reversed; that is, in myocardial infarction, the descending and ascending limbs occur during the diastolic filling and ejection phases and hence present a paradoxical sequence. This finding has also been observed by Luisada and Fleischner<sup>25</sup>. Stauffer and Jorgens<sup>37</sup> also found a similar abnormality in 2 histories of ventricular aneurysm. These workers found that the most rapid outward movement of the aneurysmal wall occurred during the isometric contraction and early systolic ejection phases of the cardiac cycle. During the latter part of systole the wall remained relatively stationary, only to move sharply inward shortly after the closure of the aortic valve. They also interestingly observed that roentgen kymograms of these patients demonstrated the changes found in the electrokymograms only with the greatest difficulty.

Although paradoxical movement of the ventricular border in the great majority of instances probably indicates the presence of a myocardial infarct, Gillick<sup>11</sup> has observed a few instances of the phenomenon in normal healthy young adults. Gillick has explained the observation by postulating that the shortening of the interventricular septum during systole is greater than usual and that almost the entire decrease in the volume of the ventricular chambers is due to this septal hyperactivity. As a result the ventricular wall actually is displaced

outward during systole. Whether or not this explanation is sound must await further observation.

Another instance where electrokymography appears to yield valuable information concerning the status of the myocardial muscle is in the relatively great precision with which it permits the measurement of the isometric relaxation phase of the cardiac cycle. Physiologists, including Wiggers<sup>39</sup> and Burstein<sup>5</sup>, have believed for some time that this phase provides an excellent index of the relaxation process and of the functional condition of the myocardium. Unfortunately, clinical methods to measure the duration of this phase have not heretofore been available. Luisada, Romano and Torre<sup>26</sup> working with normal subjects and with patients with mitral stenosis, and Boone, Randak, Ellinger and Oppenheimer<sup>4</sup> working with normal and hypertensive individuals and with patients having myocardial infarction and bundle-branch block, appear not only to have strikingly confirmed the concepts of Wiggers and Burstein but also to have demonstrated that electrokymography is a simple and reliable method for measuring the duration of the phase. The observations of Boone and his group indicate that the duration of the isometric relaxation phase in the normal healthy adult ranges from 0.06 to 0.16 second with 71% of the observed cases falling between 0.10 to 0.13 second. The pathological group on the other hand exhibited isometric relaxation times ranging from 0.10 to 0.22 second, with 71% falling between 0.15 to 0.18 second.

The causes of increased duration of isometric relaxation have been the subject of considerable conjecture by physiologists. Three factors have been suggested to account for the phenomenon. These include: *a*, the inherent rate of muscular relaxation. *b*, the intraventricular pressure at the onset

of isometric relaxation, and *c*, the intra-atrial pressure at the end of isometric relaxation.

In hypertension Boone and his co-workers believe that the increased intraventricular pressure at the end of systole results in a greater pressure differential between the ventricle and auricle and hence a prolongation of the isometric relaxation phase. Later as the hypertrophy of the musculature progresses and its nutrition becomes impaired, the inherent rate of relaxation becomes slower. It was also found in 2 cases with congestive failure that the duration of the isometric relaxation phase returned to normal levels. It is believed that this reversion is caused by a decrease in the intraventricular pressure at the end of systole as compared to the compensated hypertensive state. Also the elevated intra-atrial pressure in the decompensated state probably terminates the phase prematurely by reducing the differential pressure between ventricle and auricle still further.

In cases of bundle-branch block and myocardial infarction it appears that the principal factor responsible for the prolongation of the isometric relaxation phase is an increase in the inherent rate of muscular relaxation following metabolic and structural changes in the ventricular muscle. Boone and his co-workers also speculated that the prolonged relaxation phase might be a compensatory measure to maintain adequate coronary blood flow since Gregg and Green<sup>13</sup> have demonstrated a large coronary blood volume flow during this phase of the cardiac cycle.

Some rather striking changes of the ventricular electrokymogram have been observed by Gillick and Reynolds<sup>10</sup> in cases of constrictive pericarditis. The ascending limb of the rapid diastolic filling phase commences in its normal fashion but, after completing a portion

of its excursion, it ends abruptly in a sustained plateau which persists until the ejection phase of systole begins. Apparently the pericardium sharply restricts the outward motion of the ventricular wall soon after the ventricle has begun to fill. In a review of the electrokymograms presented by Stauffer and Jorgens<sup>37</sup> it is interesting to observe that their Case VI presents such a pattern at the left lower ventricular border and it therefore may be presumed that the primary diagnosis was a constrictive pericarditis rather than the tricuspid regurgitation that was reported. The other clinical findings in this case are also quite consistent with this disease.

Stauffer and Jorgens<sup>37</sup> also noted abnormalities of the aortic electrokymogram in patients with interatrial septal defects. A rather broad plateau at the height of the curve plus an unusually deep incisura were observed. Unfortunately these tracings were not published in their communication and it is therefore difficult to judge how striking the changes were. Stauffer and Jorgens explained their finding on the changed hemodynamics associated with the intracardiac shunt and transmitted motion from the adjacent enlarged pulmonary artery.

Luisada and Fleischner<sup>27</sup> have recently reported characteristic changes of the left auricular electrokymogram in 23 patients with lesions of the mitral valve. The normal electrokymogram of the left auricle as found by these workers consists of: 1, a sharp presystolic downward limb whose trough coincides with the closure of the mitral valve, 2, a serration of inconstant amplitude during systole, and 3, an ascending limb of variable slope during early diastolic collapse. In the cases with mitral regurgitation, this normal pattern was interrupted by a steep expansile wave at the beginning of ventricular systole which ended in a

broad plateau which persisted until the opening of the mitral valve. The wave then descended sharply at the beginning of ventricular diastole. The changes are the result of mitral regurgitation.

Interesting use of electrokymography in the study of asynchronism of the right and left ventricles has recently been reported by several workers<sup>7,8,24</sup>. Chamberlain and his co-workers made consecutive electrokymograms of the pulmonary artery and of the aortic arch with the carotid sphygmogram. The time interval between the onset of pulmonary ejection and the onset of aortic ejection was determined by using the carotid sphygmogram as a standard of reference. In normal subjects asynchronism of ejection occurred in 51 of 68 subjects. Left ventricular ejection led by 0.01 to 0.03 sec. in 32 cases; right ventricular ejection led by 0.01 to 0.03 sec. in 19 cases.

In patients with intraventricular block, the asynchronism was strikingly accentuated. In 6 patients with right bundle-branch block the onset of the ejection phase of the right ventricle lagged behind the left ventricle from 0.04 to 0.05 second. In 9 patients with left bundle-branch block the left ventricular ejection lagged behind the ejection phase of the right ventricle from 0.04 to 0.07 second. In a tenth patient the difference was 0.03 second (the upper limit of normal).

The asynchronism which normally occurs between the right and left ventricles has been used by Gillick<sup>11</sup> to determine the source of the pulmonary blood supply in a case of unilateral pulmonic stenosis. He was able to demonstrate beautifully that on the normal side of the chest the pulmonary pulse waves were synchronous with those of the right ventricle, whereas on the stenotic side the pulsations were synchronous with those of the aorta. The blood supply to the lung on the stenotic side was therefore through

bronchial collateral arteries. This case seems to indicate that electrokymography may be able to solve the difficult problem of ascertaining before surgery the pulmonary blood supply in patients with varying grades of pulmonic stenosis (*i.e.*, patients with such congenital anomalies as the tetralogy of Fallot).

Another physiologic investigation using electrokymography has recently been published by Kay, Wood, Zinsser and Benjamin<sup>22</sup>. These authors studied the validity of electrokymograms for measuring the diametric change of the aorta and pulmonary artery during circulatory disturbance. In their investigation, voluntary straining was employed as a test circulatory disturbance. It was found that qualitatively the changes in the amplitudes of the electrokymographic tracings paralleled coincident changes in pulse pressure in the brachial artery and that the amplitude of aortic pulsations, after correction for pulse rate, have a quantitative relationship to pulse pressure approximating that which would be expected between aortic diameter change and pulse pressure. More than a good approximation cannot be expected however since differences in the diameter of the aorta during and after straining cause the aorta to have different Roentgen-ray transmissions. Therefore, a given border movement of the aorta under the 2 conditions will produce electrokymograms of different amplitude.

Finally, what probably will prove one of the most important applications of electrokymography has just been proposed by Ring, Balaban and Oppenheimer<sup>30</sup>. These workers have conducted a study in which the amplitudes of the electrokymograms taken over the body of the left ventricle were correlated with the cardiac output, as determined by the ballistocardiographic method of Starr<sup>36</sup> in 28 patients. A surprisingly good correlation

was found. It is rather unfortunate, however, that the ballistocardiographic method was employed as a standard of reference in this investigation as it is thought by many to be less reliable than the methods of Fick and Stewart. If further studies, using these latter methods of reference, demonstrate an equal or better correlation between cardiac output and the electrokymogram, a simple clinical procedure for determining this parameter will at last be at hand. Since ventricular electrokymograms resemble very closely the volumetric changes that occur in the heart, there is good reason to expect

that an excellent correlation will be obtained.

From the material that has been reviewed in the foregoing paragraphs, it is evident that the electrokymograph is a radiologic tool of rapidly developing significance. With several other recent developments it is raising the curtain on a new era of roentgen investigation, an era of physiologic rather than anatomic study. It will be interesting to pursue the many new applications of electrokymography that doubtless will occur in the years to come. The method has certainly shown remarkable potentialities in the few years since its inception.

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# BOOK REVIEWS AND NOTICES

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**THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS.** Edited by EDWARD W. HAYES, M.D., *et al.*, American College of Chest Physicians. Pp. 480; 74 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, \$9.50.

THIS book has been prepared by an editorial committee of the American College of Chest Physicians. Its purpose is to present in a concise manner fundamental information on the cause, prevention, diagnosis, treatment and control of tuberculosis. The committee calls attention to the diversity of material and sources with which medical students, practicing physicians and teachers should be familiar in order to obtain a working knowledge of tuberculosis, and has attempted to save them the effort of extensive search through the literature by bringing together in a single volume principal facts in the wide range of subject material covered. The result has been a successful presentation of the chief aspects of tuberculosis treatment and control, with emphasis on modern developments. The 26 chapters cover in commendable fashion basic knowledge in the fields of anatomy, bacteriology, immunology and pathology, physical, laboratory and Roentgen-ray diagnosis, treatment by sanatorium methods, psychosomatic aspects of the disease, bronchial tuberculosis, minor and major surgical procedures in the treatment of tuberculosis, public health aspects of its control, tuberculosis of special systems and various complications. A useful bibliography is appended. The book can be highly recommended as a ready reference for information in the various fields of tuberculosis. E. L.

**A TEXTBOOK OF HISTOLOGY.** By ALEXANDER A. MAXIMOW, Late Prof. of Anatomy, and WILLIAM BLOOM, Prof. of Anatomy, Univ. of Chicago. 5th ed. Pp. 700; 562 ills., 32 in color. Phila.: W. B. Saunders, 1948. Price, \$8.50.

THIS 5th edition follows in its main outlines the plan of earlier editions. Recent advances have been incorporated without increasing the size of the book, and examples of the newer histochemical techniques have been judiciously chosen. Both features are in keeping with the general nature of the subject, allowing presentation of the more fundamental aspects of histology in a comprehensive

and readable manner. The paper, type and illustrations are of unusual excellence. C. B.

**HINDU MEDICINE.** By HENRY R. ZIMMER. Ph.D., Formerly Prof. of Sanskrit, Univ. of Heidelberg. Edited by LUDWIG EDELSTEIN. Ph.D. Pp. 201. Balt.: Johns Hopkins Press, 1948. Price, \$4.00.

THIS is in no sense an account of Hindu medicine through the ages, or even through ancient times, nor is it intended to be one. It is, however, an interesting view of the high points of pre-Aryan, Vedic, Buddhist, Tantric and Ayurvedic philosophy in relation to medical theories and practices closely correlated with the pervading myths and philosophy of Hinduism.

THE 7th series of the Noguchi Lectureship on the History of Medicine was given by Professor Zimmer in 1940. Three years later he died before his revision of the material for publication had been completed. The first 2 of the 3 lectures are published substantially as they were found in his papers, even though fragmentary. To augment the analysis of Hindu medicine the editor has contributed a lengthy Preface outlining Zimmer's concept of Hindu culture, and has included, as an act of piety, as many as possible of the scattered notes and outlines for the missing chapters. A stimulating and valuable combination of Hindu medical lore, mysticism and philosophy emerges. E. K.

**SKIN DISEASES IN GENERAL PRACTICE.** By F. RAY BETTLEY, M.D., Middlesex Hospital, London. Pp. 260; 96 ills. London: Eyre & Spottiswoode, 1949. Price, 21 s.

HERE Bettley has undertaken to do what many dermatologists have wanted to do: write a book for the general practitioner covering only those diseases which are common and discussing them adequately enough to be practical. Although the author has done a yeoman's job, the selection of topics to be discussed will not meet the approval of all authorities, since determination of what is common will vary with the individual specialist as well as with the general practitioner because of differences in the composition of their practice. On the whole, however, in spite of the omission of some diseases.

others not uncommon but which pose difficult situations to the practitioner (e.g., urticaria, erythema multiforme) are hardly mentioned. On the other hand, it might be desirable to omit detail on certain therapeutic procedures requiring special skill and training (e.g., thorium-X).

This is one of the better handbooks recently published, and it merits wide consideration. H. B.

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**HUTCHISON'S FOOD AND THE PRINCIPLES OF DIETETICS.** Revised by V. H. MOTTRAM, M.A. (Cant.), and GEORGE GRAHAM, M.D. (Cant.), F.R.C.P. (Lond.). 10th ed. Pp. 727. Balt.: Williams & Wilkins, 1948. Price, \$6.75.

DIETETICS and nutrition are reverse sides of the same coin. This is a detailed survey of human foods and their composition which correlates this information with the current understanding of what happens to the separate components of food during digestion and endogenous metabolism. Emphasis is given to both psychologic influences and individual variation factors which most American textbooks tend to underestimate. This new tenth edition discusses much of the new data which has accumulated during—and largely because of—the war years. Like many English texts it is eminently readable.

I. W.

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**SYPHILIS: ITS COURSE AND MANAGEMENT.** By EVAN W. THOMAS, M.D., Prof. of Clinical Medicine, New York Univ. College of Medicine. Pp. 317; 59 ills. New York: Macmillan, 1949. Price, \$5.50.

ANY present-day exposition on the course and management of syphilis must be tentative and the author a person of great courage to be willing, as Dr. Mahoney hopes in the introduction to this volume, to "build a series of revisions which will carry the disease through the period of change and which will attempt a final evaluation of the events now taking place." As a seconder to this hope, the Reviewer believes Dr. Thomas has produced a concise review of the status of syphilis today and while he does not accept all the conclusions reached, he feels that this volume will at least fulfill the purpose of stimulating thought and further investigation, but because of the complicated mode of presentation, it is far from the mark of giving "busy individuals a practical understanding of the principles underlying the modern diagnosis and treatment of syphilis." For the Specialist, however, there is much to commend this book. While most of the data

presented are interpreted personally by Dr. Thomas, he has sought assistance of many able authorities including Dr. Theodore Bauer, Dr. Charles R. Rein, Dr. Bernhard Dattner and Dr. Joseph Earle Moore.

The section on Interpretation of Quantitative Serologic Tests for Syphilis is probably the most detailed compilation the Reviewer is aware of. To counterbalance this worthy service there are many views which may be misleading to the less critical practitioner. For example: the experience of the Author regarding the location of mouth spirochetes only at the margin of the gums, thus discrediting the validity of darkfield results from specimens removed from other oral sites; his views on reinfection tend a little on the side of uncritical definition since his only absolute criterion of reinfection is the development of a new chancre at a different site from the original one (p. 39).

The Reviewer feels that some expansion of the text and attention to the loose ends produced by the present "shakedown cruise" will lead eventually to the production of one of the outstanding volumes on syphilis.

H. B.

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**CARDIOLOGY.** By WILLIAM EVANS, M.D., Physician to the London Hospital. Pp. 310; 269 figs. New York: Paul B. Hoeber, 1948. Price, \$7.50.

In the preface Dr. Evans states that this book was written for medical students in preparation for higher examination and for busy practitioners. It was not intended to compete with standard text-books. The subject matter is large and the discussion is short. Physiological and pathological aspects of heart disease are considered briefly and many American electrocardiographic aspects of myocardial infarction are lacking. The roentgenographic coverage is excellent. I do not believe that this work is sufficiently detailed. The book is clearly written, is well printed and is excellently bound. H. F.

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**DISEASES OF THE LIVER, GALLBLADDER AND BILE DUCTS.** By S. S. LICHTMAN, M.D., Ass't. Prof. of Clinical Medicine, Cornell Univ. Medical College. 2d ed. Pp. 1135; 147 ills., 4 in color. Phila.: Lea & Febiger, 1949. Price, \$18.00.

THIS textbook is a comprehensive work dealing not only with the diseases, as its title suggests, but also with the anatomy and physiology of the liver and biliary structures. In addition it covers the modern techniques for the study of hepatic and biliary diseases. It has been effectively revised and the ma-

terial is presented in better order than in the original edition. An exhaustive number of references is available at the conclusion of each chapter.

The great amount of knowledge that has been accumulated during the past decade concerning hepatitis is strikingly demonstrated by comparing the brief discussion of the possible etiologies of catarrhal jaundice in the 1st edition with the 104 page chapter on viral hepatitis in this one. Liver function tests are covered in 2 ways: first, in a separate chapter concerned with their technical and physiological aspects; second, with their application to specific diseases.

The book will be of great value to anyone interested in liver disease from either the clinical or the investigative point of view.

W. S.

**MEDICAL ETYMOLOGY.** By O. H. PERRY PEPPER, M.D., Prof. of Medicine, Univ. of Pennsylvania. Pp. 263. Phila.: W. B. Saunders, 1949. Price, \$5.50.

EVERY medico—student or M.D.—should be exposed to this novel work. Once past a necessarily repelling title, many more than the followers of semantics will soon find enough of interest or value to lead them to proceed further. The author's well-known combination of an excellent sense of proportion and practicality with a dexterity of presentation and lightness of touch is in welcome contrast to the usual medical text. Humor happily keeps breaking through (cp. the remarks on rigor, phrenic, prognosis, xerostomia, morgue, to mention but a few). One thinks, too, of his address at the dinner of the Association of American Physicians in 1948.

The "*Verb. sap.*" of the book's motto is more apt to be sufficient after a deviously derived meaning has been explained in this book than it is to the linguist who has a correct translation of its components but a totally incorrect definition (Cp. epithelium). Nevertheless, the etymology of a scientific word usually gives a correct idea of its meaning and in any case affords a convenient peg of association to aid the memory burdened by a flood of new and forbidding terms. To digress a little further, the layman is wrong, though perhaps excusably so, when he accuses the doctor of professional pomposity when he resorts to polysyllables to express his meaning. Who would deny that it is easier for the physician to speak of, let us say, "choleodochojejunostomy" instead of "the operation of making an opening between the bile duct and the empty part of the bowel?"

Dr. Pepper is over-modest in disclaiming originality and completeness of material. His approach is original and such a work could never be complete.

The less than 4000 terms are presented in some 15 and 20 categories, such as Anatomy, Psychiatry, Radiology, but all can be readily found with the help of the good index. One inevitably misses some words which could profitably have replaced others that have obvious meanings or derivations or are excessively rare or vary but little from words that have been included. Inevitably, also, one disagrees with some derivations or points of view, such as that on the use of eponyms; but at the same time one is impressed with the author's knowledge of words and their history, or, what amounts to the same thing, his ability to uncover and utilize such knowledge. We can hope that his continued interest will lead before long to another bigger and even better edition.

E. K.

**HIPPOKRATES-FIBEL.** Von Dr. med. RICHARD KAPFERER, München und Bad Wörishofen. Pp. 355. Stuttgart: Hippokrates-Verlag, Marquardt & Cie., 1949. Price, D.M. 16.50.

FROM his lengthy translation of the complete works of Hippocrates into modern German (1934-1940), Dr. Kapferer has selected for this Fibel, or Primer, several hundred passages that are calculated to throw light on the ways of thinking and the actual medical knowledge of the Hippocratic School. The extracts vary in length from a single line to a page or more, and are grouped under 69 headings such as the Oath; the Aphorisms; Diet; Airs, Waters, Places; Hemorrhoids.

For the not inconsiderable number who would like to know more about details of Hippocratic medicine but are unable, or think they are unable, to find the necessary time to search through the Hippocratic Corpus, such a book as this is better able than its parent to provide the half loaf that is proverbially better than none.

The volume has an interesting provenance. Published and copyrighted by Marquardt & Co., of Stuttgart in 1943, it was printed at Breda in Holland on war-paper (date not given), and reaches us for review in 1949.

E. K.

**STUDIES ON HOOKWORM DISEASE IN SZECHWAN PROVINCE, WEST CHINA.** By K. CHANG and Co-workers. The American Journal of Hygiene Monographic Series, No. 19, May, 1949. Pp. 152; 34 figs. Balt.: Johns Hopkins Press, 1949. Price, \$3.00.

THE occurrence of hookworm disease in any population depends upon: 1, human infection; 2, soil pollution; 3, an environment favorable to the development of infective hookworm larvae in the soil, and 4, human contact with the infected soil adequate to continue the parasite in its host. In many parts of the world hookworm disease results from promiscuous defecation by people near their houses or in other often frequented sites. In China, however, hookworm infection is more of an occupational disease of the farming population. For in China human excrement is carefully conserved and used as fertilizer. It is not so much the use of human feces to fertilize crops that maintains the infection but the particular methods employed in planting, cultivation or harvesting. These methods may vary with the locality. Thus an understanding of the epidemiology and control of the parasite must come from a complete study of agricultural practices. In this monograph Dr. Chang and his associates have presented their studies of hookworm disease and its control in a large and important province of China. The book is well written, adequately illustrated and an interesting account of their work.

H. R.

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ARTHRITIS AND ALLIED CONDITIONS. By the Late BERNARD I. COMROE, M.D. Edited by JOSEPH L. HOLLANDER, M.D., Univ. of Pennsylvania. 4th ed. Pp. 1108; 370 ill. Phila.: Lea & Febiger, 1949. Price, \$16.00.

THIS edition of Comroe's book on arthritis has been completely revised and brought up to date by Dr. Hollander of the University of Pennsylvania Hospital. There are 17 contributors to this excellent book of over 1100 pages in which the illustrations and bibliography are well chosen and carefully screened.

There might be some criticism of Part X, for here the book departs from its chosen role as a treatise on arthritis and considers in detail such subjects as internal derangement of the knee joint, cervical rib, Dupuytren's contracture, and others. While one may sympathize with the Authors' dilemma in delineating the scope of this book, one would feel that this chapter is almost wholly a discussion of orthopedic conditions, not directly related to arthritis, or at least no more so than scores of other affections of orthopedic interest.

The book, however, represents a valuable contribution, and the editor and his associates deserve high praise.

P. C.

NUTRITION AND DIET IN HEALTH AND DISEASE. By JAMES S. MCLESTER, M.D., Prof. of Medicine, Univ. of Alabama. 5th ed. Pp. 800. Phila.: W. B. Saunders, 1949. Price, \$9.00.

THE late world conflict and its associated dislocation stimulated a considerable volume of research in human nutrition. The results of much of this work have been published since the last edition of this book appeared 6 years ago. During the same period there have been significant studies of dietary factors in the macrocytic anemias, in cirrhosis and other diseases of the liver, in antibody formation, and in surgery and wound healing. Professor McLester has rewritten much of the book to bring it into line with the newer points of view or has incorporated new material in appropriate parts of the text. The chapters, Feeding of Infants by Professor Philip Jeans, and Nutrition in Industry by Dr. Robert S. Goodheart also have been rewritten. A new chapter, Feeding of Surgical Patients by Dr. Charles C. Lund, has been added. This edition compares well with earlier ones.

H. R.

## NEW BOOKS

*Help Yourself to Better Sight.* By MARGARET DARST CORBETT. Pp. 218. New York: Prentice-Hall, 1949. Price, \$2.50.

WRITTEN in support of the Bates system of improving vision by relaxing.

*Headaches.* By NOAH D. FABRICANT, M.D. Pp. 149. New York: Farrar, Straus, 1949. Price, \$2.50.

THIS is as useful as such books for the layman can be in answering baffling questions where a visit to the physician is not needed, and in steering the patient to him when it is.

*Fundamental Considerations in Anesthesia.* By CHARLES L. BURSTEIN, M.D., Instructor in Anesthesia, New York Univ. College of Medicine. Pp. 153. New York: Macmillan, 1949. Price, \$4.00.

IN this small book, the author has attempted to discuss many of the main problems that beset the anesthesiologist such as abnormalities of respiration; laryngeal spasm; physiological and pharmacological considerations of the patient in shock; celiac plexus reflex; cardiac arrhythmia and gastro-intestinal autonomic reactions. Unfortunately, many of the statements that are made are undocumented and the discussions are too brief to be of real benefit. However, the subject matter should be thought provoking to the student of anesthesiology.

J. E.

*George R. Minot Symposium on Hematology.* Edited by WILLIAM DAMESHEK, M.D., and F. H. L. TAYLOR, Ph.D. Pp. 984. Illustrated. New York: Grune & Stratton, 1949. Price, \$12.00.



*Medical Clinics of North America* New York number, May, 1949. *Symposium on Cardiovascular Diseases, especially Hypertension* Pp. 607-922 Phila.: W. B. Saunders, 1949 Price, \$15.00 a year.

In this review the coverage of the practical aspects of hypertensive disease is at times incomplete in that some of the newer drugs have been omitted from the discussion on treatment. However, it is the Reviewer's opinion that the symposium is to be favorably recommended. It is useful in concisely presenting a discussion of the variable clinical course of hypertensive disease. This includes psychosomatic factors, role of the carotid sinus, organic vascular disease, management of the hypertensive disease of pregnancy, and the controversial subjects of capillary fragility and low sodium diet in clinical hypertension. The merits of various types of sympathectomies are discussed. C. C.

*The Yearbook of Psychoanalysis* Edited by SANDOR LORAND, M.D. Vol. IV. Pp. 356 New York: International Universities Press, 1949. Price, \$7.50.

TWENTY-TWO unrelated articles by as many authors, together with 2 pages of selected reading

*Psychosexual Development in Health and Disease.* Edited by PAUL H. HOCH, M.D., and JOSEPH ZUBIN, Ph.D., Columbia Univ. Pp. 283. New York: Grune & Stratton, 1949. Price, \$4.50.

*Your Child Makes Sense.* By EDITH BUNBAUM, Ph.D. Foreword by ANNA FREUD. Pp. 204 New York: Internat'l Univ. Press, 1949 Price, \$3.25.

*Psychodiagnosis.* By SAUL ROSENZWEIG, Ph.D., Assoc. Prof., Psychology and Neuropsychiatry, Washington Univ., St. Louis, Mo., and KATE LEVINE KOGAN, Ph.D. Pp. 380. New York: Grune & Stratton, 1949. Price, \$5.00.

The psychodiagnostician relies in his work on tests which have been standardized. This book emphasizes the concrete materials and operations

of the clinical psychologist rather than abstract principles of psychology. Illustrative case-histories are included. The book will be found to be both informative and useful

W. P.

## NEW EDITIONS

*Papers on Psychoanalysis.* By ERNEST JONES, M.D. 5th ed. Pp. 501. Balt.: Williams & Wilkins, 1949. Price, \$8.50.

*Hematology.* By WILLIS M. FOWLER, M.D., Prof. of Internal Medicine, Univ. of Iowa. With a Chapter by ELMER L. DEGOWIN, M.D. 2d ed. Pp. 535; 184 ills., 8 color plates. New York: P. B. Hoeber, 1949 Price, \$8.50.

AMONG the advances recorded in this edition are "The use of folic acid in various diseases, particularly sprue, the use of urethane in the treatment of leukemia and of nitrogen mustard in the lymphomas, the use of radiophosphorus in the treatment of polycythemia and leukemias . . ." DeGowin's completely revised chapter on Transfusion gives a good consideration of the Rh factor and other blood groups

*Fundamentals of Internal Medicine.* By WALLACE MASON YATER, M.D., Director, Yater Clinic, formerly Prof. of Medicine, Georgetown Univ., etc. 3d ed. Pp. 1451, 315 ills. New York: Appleton-Century-Crofts, 1949 Price, \$12.00.

In these days when it is practically impossible for standard medical textbooks to keep up to date, this new edition through numerous corrections and additions successfully avoids congenital obsolescence. In general, it adheres to the author's original plan of presenting "the minimum amount of knowledge of clinical medicine a medical student or general practitioner should have." While such a text offers less to the post-graduate student or specialist, it probably has its place in teaching and seems to be liked by those for whom it is intended H. Z

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# THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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## ORIGINAL ARTICLES

### THE OCCURRENCE OF ATHEROMATOUS LESIONS AFTER CAUTERIZATION OF THE AORTA FOLLOWED BY CHOLESTEROL ADMINISTRATION\*\*

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AND

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DISTURBANCES in the vascularity of the aortic wall cause disease of the aorta<sup>1,5,6,8</sup>. In the dog, obstruction of the vasa vasorum of the ascending aorta leads to medial necrosis and its sequelae, *viz.*, aneurysm formation, dissecting aneurysm and spontaneous rupture<sup>5</sup>. It was, therefore, felt that the tendency toward atheroma formation was related, among other things, to the state of the vasa vasorum. This was tested in the dog. The vasa of the dog are extremely well developed<sup>6,7</sup>, and this may be one of the reasons for the known difficulty in producing atheromatosis in this animal. In this study, therefore, some of the vasa vasorum were destroyed and a hypercholesterolemia was superimposed for a period of months. The effect of this combination was analyzed at necropsy.

PROCEDURE. A total of 14 adult dogs were used. In 8 animals the ascending aorta was cauterized as previously described<sup>5</sup> so as to interrupt part of the vascular supply to the aortic wall. In 6 animals, cautery was omitted.

Six of the 8 dogs subjected to cauterization received cholesterol intraperitoneally and orally; 2 of these in addition received oral thiouracil. One animal received cholesterol and thiouracil only by mouth, and 1, as a control, received only oral thiouracil. Two of the 6 animals without cauterization received cholesterol intraperitoneally and orally, 3 received oral cholesterol and thiouracil, and 1 received only oral thiouracil.

About 10 gm. of cholesterol were administered orally per day, made up as a 10% mixture in cottonseed oil and mixed with the  $\frac{1}{2}$  to 1 lb. of meat fed daily. For intraperitoneal administration, 30 to 60 cc. of a specially prepared emulsion of cholesterol containing 2 to 3% cholesterol was injected under sterile precautions, 3 to 6 times a week. The cholesterol emulsion was prepared according to the method of Cole, Clark and Womack<sup>2</sup>. Cholesterol was dissolved in ether, 12 gm. to 200

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† The department is supported in part by the Michael Reese Research Foundation.

\*\* Aided by the Life Insurance Medical Research Fund.

cc.; this solution was added to 400 cc. of tap water containing 4 gm. of sodium oleate. During this mixing process, the solution was constantly shaken. The oleate-cholesterol mixture was then dropped very slowly into a current of steam under 2 lbs. pressure. In this way the ether is completely evaporated and a fine emulsion results which is stable for a period of several weeks. Thiouracil, 0.5 to 0.8 gm. per day depending on the animal's

size, was given in gelatine capsules. In most instances, it was readily accepted by the animal; in a few, forced feeding was necessary.

**Results.** Table 1 summarizes the results obtained. The blood cholesterol levels given are the highest values in each animal. The normal levels found

TABLE I.—SUMMARY OF PERTINENT DATA

| <i>Dog No.</i>   | <i>Treatment</i>  | <i>Duration of treatment</i> | <i>Development of atheroma</i> | <i>Highest blood cholesterol mg. per 100 cc.</i> |
|--|---|------------------------------|--------------------------------|--|
| <b>Dogs Without Coagulation of the Aortic Adventitia</b> |   |                              |                                |  |
| 9814   | Cholesterol feeding, intraperitoneal injection of cholesterol; no thiouracil.         | 4 months                     | none                           | 360  |
| 0419   | Cholesterol feeding, intraperitoneal injection of cholesterol; no thiouracil.         | 4 months                     | none                           | 430  |
| 9504   | Cholesterol feeding and thiouracil feeding.   | 11 months                    | none                           | 370  |
| 9455   | Cholesterol feeding and thiouracil feeding.   | 3 months                     | none                           | 190  |
| 9805   | Cholesterol feeding and thiouracil feeding.   | 7 months                     | none                           | 260  |
| 0411   | Thiouracil feeding only.  | 7 months                     | none                           | 330  |
| <b>Dogs with Coagulation of Aortic Adventitia</b>        |   |                              |                                |  |
| 9338   | Cholesterol feeding, intraperitoneal injection of cholesterol; no thiouracil.         | 5 weeks*                     | none                           | 240  |
| 9390   | Cholesterol feeding, intraperitoneal injection of cholesterol; no thiouracil.         | 1 day*                       | none                           |  |
| 9342   | Cholesterol feeding, intraperitoneal injection of cholesterol; no thiouracil.         | 20 weeks                     | positive                       | 380  |
| 9449+  | Cholesterol feeding, intraperitoneal injection of cholesterol; no thiouracil.         | 12 weeks                     | none                           | 230  |
| 9866   | Cholesterol feeding, intraperitoneal injection of cholesterol and thiouracil feeding. | 12 weeks                     | positive                       | 360  |
| 9477   | Cholesterol feeding, intraperitoneal injection of cholesterol and thiouracil feeding. | 5 weeks*                     | none                           | 200  |
| 9333   | Cholesterol feeding and thiouracil feeding.   | 10 months                    | none                           | 320  |
| 9514+  | Thiouracil feeding only.  | 12 months                    | none                           | 280  |

+ Cauterization not successful in producing necrosis of media, presumably because of adequate collateral circulation.

\* Animals died within 5 weeks or less after operation.

in these animals were 50 to 100 mg. per 100 cc. The maximum levels of from 190 to 430 mg. were attained after 2 to 3 weeks administration of the cholesterol; thereafter the blood levels became stable or declined somewhat.

Two of the animals with cauterized aortas (9449, 9514) failed to develop medial necrosis or other expected gross or histological changes, apparently due to an adequate collateral vasa vasorum circulation<sup>5</sup>. One of the animals cauterized (9390) lived only 1 day post-operatively. Two of the animals with cauterized aortas (9338, 9477) lived 5 weeks postoperatively and showed the expected medionecrotic changes in the aorta<sup>5</sup>; however, the time of survival was apparently too short for the occurrence of atherosclerotic lesions. These 5 of the 8 animals which either did not show the primary necrotic lesions expected or lived too short a period of time on the special feeding, will not be considered further. None of the 6 control animals showed any histological or gross evidence of atheromata anywhere in the aorta.

The remaining 3 animals (9333, 9342, 9866) merit detailed description: In all 3, the parietal pericardium and right auricular appendage were adherent to the coagulated part of the adventitia. On section, greyish areas were seen in the media of the ascending aorta extending into the intima. Microscopically these greyish areas corresponded to an irregular mesh-work of fibrous tissue in the middle and inner third of the media; intimal proliferation was marked above these areas.

In dog 9333 there were no other significant changes seen throughout the entire aorta.

In dog 9342 subendothelial and medial lipid deposits, as well as several foci of old healed medial necrosis were seen microscopically (Figs. 1 and 2); grossly calcific nodules could be

observed protruding into the lumen from the aortic wall near the edges of the aortic valves.

In dog 9866 a small aneurysm was observed in the ascending aorta 2 cm. above the aortic valves. The aneurysm measured  $1\frac{1}{2}$  by 1 cm. and showed slightly raised yellowish-grey areas in the intima around the edges of the aneurysm nearest the aortic valves (Fig. 3). On section these areas extended into the media. In addition there were calcific areas in the media (Fig. 4). Microscopically lipid deposits could be seen in the subendothelial layer and in the inner third of the media. An atheromatous ulcer involving the intima and media was present with calcium deposition in the altered media resembling lesions seen in human arteriosclerosis (Fig. 5).

**Discussion.** Our results show that the addition of exogenous cholesterol with or without thiouracil which is associated with only a moderate hypercholesterolemia may lead to the development of atheromatous lesions within 3 to 5 months in the ascending aorta in the region in which vascularity of its wall has been interfered with experimentally. These atheromatous lesions are confined to the area with impoverished vascularity; they do not occur elsewhere in the aorta of the same animals, nor do they appear in other animals on a similar regimen but without such disturbances in the vasa vasorum. In addition other changes previously described<sup>5</sup>, including degenerative lesions, intimal proliferation, fibrotic and calcific changes of the media and aneurysm formation were seen. The atheromatous changes did not occur in 1 instance even after 10 months of cholesterol and thiouracil feeding (see dog 9333). However, such atheromatous lesions did appear in 2 instances where there was a combination of: *a*) sustained moderate hypercholesterolemia and *b*) local interfer-



FIG. 1. Subendocardial lipid deposits from ascending aorta. Hematoxylin-eosin ( $\times 95$ ).

FIG. 2. Subendocardial and medial lipid deposits from ascending aorta.  
Hematoxylin-eosin ( $\times 95$ ).

FIG. 3. Aneurysm formation in the ascending aorta. Atheroma formation and lipid deposits around the edges of the aneurysm and near the valves. Calcifications of the aorta near the commissures of the valves.



FIG. 4. Calcific areas in the media. Hematoxylin-eosin (x 95).

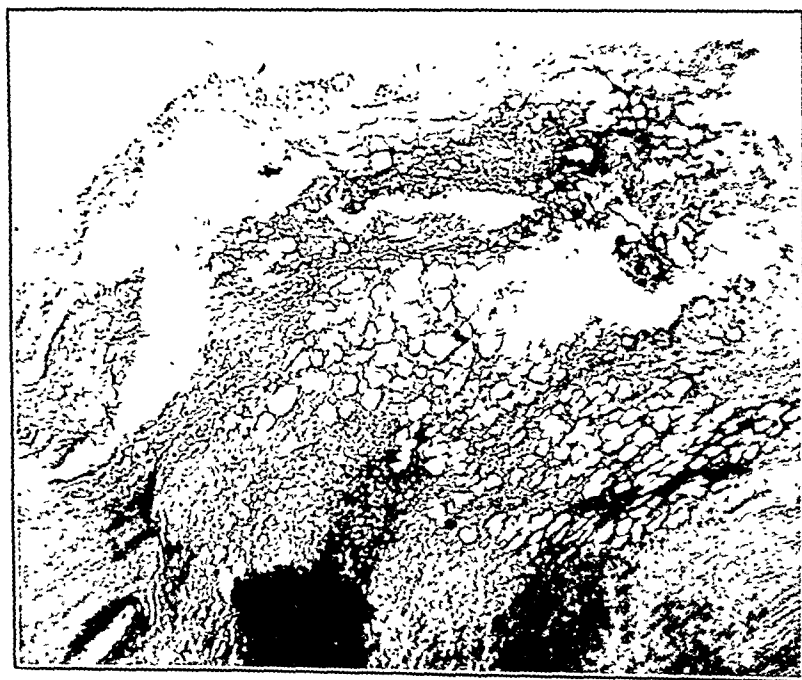


FIG. 5. Atheroma in the ascending aorta. Section taken near the edge of the aneurysm. Hematoxylin-eosin (x 95).

ence with the blood supply to the wall of the aorta.

Cholesterol feeding in rabbits and chickens induces atheromatosis of the aorta and other vessels. It has been shown in this laboratory that the rapidity and extent of development of these lesions are related to the duration and magnitude of the hypercholesterolemia<sup>3</sup>. Recently Steiner and Kendall<sup>9</sup> have shown that atheromatous lesions in the descending aorta of the dog can be produced by feeding cholesterol and thiouracil for periods up to 1 year; the cholesterol blood levels were raised up to 2000 mg. per 100 cc. Our negative results with long term cholesterol and thiouracil feeding which we are reporting do not negate the positive results of Steiner and Kendall. We did not attempt to reduplicate their experiments but used these animals as controls for our own experiments with vasa vasorum interference. We did not keep our animals on the high cholesterol diet as long nor did we raise the blood cholesterol as high as in their experiments.

Blood cholesterol levels and exogenous cholesterol are apparently not the only factors concerned in atheromatosis. For example, it has been shown in this laboratory that chickens fed on almost fat-free diet for 13 months<sup>4</sup> still develop atheroma, though not to the extent of those on an ordinary diet. In man, arteriosclerosis and atheromatosis correlated poorly with the amount of exogenous cholesterol in the diet or with the blood cholesterol levels. These facts suggest the possible operation of some other factors in the production of atheromatosis. The present report brings forth evidence that the nourishment of the wall of the blood vessels may be one such important factor.

Our present studies indicate that the difficulty of inducing atherosclerosis in the dog may be overcome by inter-

fering with this rich vascularity of the dog's aortic wall. It would follow from this that the vascularity of the aortic wall is important in producing and localizing medionecrotic, arteriosclerotic and atherosclerotic lesions. We have demonstrated that atheromatosis develops in the area with diminished vascularity in a relatively short period of time (3 to 5 months) with only a moderately raised blood cholesterol level in the dog. It is, therefore, possible that with a markedly diminished local blood supply of the aortic wall cholesterol deposits may appear under certain circumstances even with a normal blood cholesterol level.

**Summary.** 1. Of 8 dogs in which the ascending aorta had been cauterized, 1 developed atheroma within 20 weeks on being given cholesterol orally and intraperitoneally. A second dog developed atheroma within 12 weeks on the same regime plus oral thiouracil. A third dog failed to develop atheroma after 10 months of oral cholesterol and thiouracil. Three of the other dogs lived less than 5 weeks postoperatively, apparently not long enough to develop atheroma. The remaining 2 did not show medial necrosis or other degenerative lesions and so did not have the local ischemia or degeneration upon which atheroma might be expected to develop.

2. The lesions in the 2 animals with atheroma were confined to the area in which there had been interference with the vasculature of the vessel wall.

3. Six dogs without cauterization of the aorta kept on a similar regimen of cholesterol and, or, thiouracil showed no atheromatous or other pathological changes of the aorta.

4. The relationship of the state of vascularity of the aortic wall to disturbances of lipid metabolism in the pathogenesis of experimental atheroma and arteriosclerosis is stressed.

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# THE VASCULARIZATION OF THE AORTA

## II. A COMPARATIVE STUDY OF THE AORTIC VASCULARIZATION OF SEVERAL SPECIES IN HEALTH AND DISEASE\*

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IN a previous report a technique of studying the vascularity of the aorta was presented and the vascularization of the aorta in the normal dog described<sup>4</sup>. The effects of experimental interference with the vascularization of the aorta in the dog were likewise analyzed<sup>5</sup>. The present report is concerned with the results of an investigation of the comparative vascularization of the aorta in man, dog, chick, and rabbit by means of roentgenologic and microscopic techniques. For greater accuracy separate series were conducted by two observers working independently and using standardized techniques so that the semiquantitative measurements obtained could be compared.

**Methods.** The hearts and aortas were obtained postmortem and the vasa vasorum of the aorta injected in one of two ways. In the first method a glass cannula was inserted into the aorta, either at the arch or in the descending part of the aorta, depending upon the portion under study. Facing upstream, the cannula was tied firmly into place. All branches of the aorta above the cannula except the coronary vessels were ligated near their origin. In the second method a cannula facing upstream was tied

into the lumen of the right, left, or both coronary vessels. Prior to injection the coronary ostia in the sinuses of Valsalva were occluded by wet cotton to prevent leakage into the aorta.

In most instances the dogs, rabbits, and chickens were heparinized before being sacrificed. The pericardium and tissues adjacent to the heart and aorta were generally removed together with the heart and aorta.

By means of a modified Schlesinger apparatus the cannulated vessel was irrigated first with warm saline solution after which the warm, radio-opaque mixture of Dock\*\* was perfused under a pressure of 150 to 200 mm. of mercury for 20 to 30 minutes. During the first part of the injection the pressure was permitted to fall to zero several times, thereby changing the solution in the aorta and allowing better filling of the vasa vasorum. Immersion of the container in hot water kept the radio-opaque mixture warm and fluid. Ligatures or clamps controlled major leaks from the aorta. Slow oozing of the mixture from small leaks in the aorta was permitted. At the end of the injection period the specimen was packed in ice while the injection pressure was maintained. After the radio-opaque material was fixed in the vessels by the cooled, solidified gelatin, the aorta and heart were opened, the aorta separated from the heart and x-rayed. Only apparently well-injected specimens were x-rayed. The infrequency of wide departures from the average distribution in normal animals is confirmatory evidence of the success of the injections.

\* Aided by the Life Insurance Medical Research Foundation.

\*\* Two hundred and fifty grams of lead carbonate and 50 gm. of mercuric sulfide with 500 cc. water were mixed in a ball mill jar to get a fine suspension (Solution A). Then, to 500 cc. of water, 120 gm. of sucrose and 60 gm. of "Difco" Gelatine were added (Solution B). The latter was warmed to 50° C. with constant shaking. Solutions A and B were then mixed and filtered through two layers of wet cheese cloth and the mixture then placed in the icebox until needed<sup>3</sup>.

† Present address: Albany, New York.

The roentgenologic technique depended upon the type of x-ray machine used and the thickness of the specimen. Several roentgenograms of the same specimen were generally taken under slightly varying techniques to obtain the best possible detail. The following settings were found to give superior detail most consistently: kv, 30-40; ma, 100-30; time,  $\frac{1}{4}$ -1 $\frac{1}{2}$  seconds; fine focal spot; anode-film distance, 30 inches; paper film holder; and non-screen film.

Microscopic sections were then prepared from the specimens and examined to determine the degree of actual vessel filling. An attempt was made to estimate semi-quantitatively the vascularization of the ascending aorta by classifying the different aortas on the basis of number and distribution of the vasa vasorum according to the following plan: A, no vascularity observed (grade 0); B, comparatively poor vascularity (grade 1);

from the left and right coronary arteries, by vessels arising from the great vessels of the aortic arch, and by vasa originating directly from the lumen of the aorta. The vasa from these 3 sources form a rich anastomotic network. The extensive adventitial system is supplied by vasa from the coronary arteries and the large arteries of the aortic arch, while the less extensive medial system is composed of vasa arising from the adventitial network and from the lumen of the aorta. The vasa originating from the lumen of the aorta spread into the inner and middle thirds of the media. Often reaching the outer third of the media, these vasa

TABLE 1. SUMMARY OF MATERIAL EXAMINED

| Species | Type of Aorta                                 | Number of Injection Specimens |          |
|---------|---|-------------------------------|----------|
|         |   | Series 1                      | Series 2 |
| Dog     | Normal  | 60                            | 7        |
|         | Experimentally disturbed                      | 11                            | 0        |
| Human   | Premature Infants                             | 2                             | 9        |
|         | Infant (4 months old)                         | 0                             | 1        |
|         | Children and Youths<br>(1 to 18 years of age) | 4                             | 0        |
|         | Adults (20 to 80 years of age)                | 12                            | 6        |
| Chicken |   | 24                            | 7        |
| Rabbit  |   | 12                            | 11       |
| Total   |   | 125                           | 41       |

C, comparatively fair vascularity (grade 2); D, comparatively good vascularity (grade 3); E, comparatively excellent vascularity (grade 4).

Several rabbits and chickens were injected in toto. These were anesthetized, heparinized, and then bled from the femoral artery while intravenous isotonic glucose was administered. After exsanguination the radio-opaque mixture was injected retrograde through the femoral artery. A few specimens were dehydrated by immersion in increasing concentrations of ethyl alcohol and then cleared with oil of wintergreen so that the distribution of the vessels could be studied grossly.

**Results.** The number of preparations examined in both series is listed in Table 1. The composite findings in each of the species follow:

**Dog.** The ascending aorta of the normal dog is supplied by vessels arising

from the lumen of the aorta could be seen to anastomose with the adventitial vessels. Microscopically, numerous small openings (stomata) with diameters too small to be injected by the mixture were seen. The adventitial plexus became progressively less extensive caudad while the number of intimal vessels appeared to increase.

In 11 dogs the vascularity of the ascending aorta was disturbed experimentally<sup>5</sup>. Absence of vascularity of the affected area appeared in animals showing medionecrosis, spontaneous rupture of the aorta, and dissecting aneurysm. In the dogs in which the medionecrotic lesions healed, a marked increase in number and irregularity of the vascular network of the coagulated

region was found 6 weeks after the experimental injury.

The majority of the dog specimens demonstrated comparatively excellent vascularity (grade 4) although some had a less extensive vasa vasorum supply. In a number of specimens the very vascular and very well injected cardiac fat pad surrounding the root of the aorta was removed with scissors so that the roentgenograms would give an index of the vascularity of the aorta without superimposition of these vessels. Anatomically and physiologically the fat pad does contribute to the vascularization of the aorta.

observed in the atheromatous lesions of man. A few vasa were occasionally seen in the middle third of the media, but no direct vessels from the intima were found with the exception of stomata. When the ductus arteriosus was patent in the infants, vasa between the aorta and pulmonary artery were visible grossly and roentgenologically. The pulmonary artery generally showed better vascularity than the aorta when it was injected in several cases.

*Chicken.* In chickens the vascularity of the aorta was comparatively less than in the dog and human, but somewhat more than in the rabbit. Some

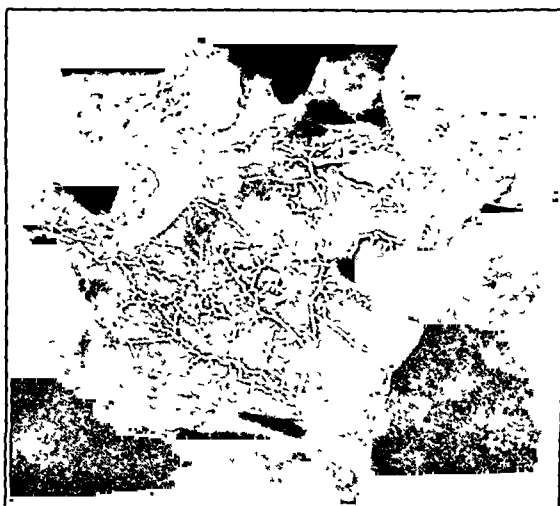


FIG. 1. Roentgenogram of the dog's aorta after injection (actual size) showing the comparative excellent vascularity of its ascending portion. In the middle of the lower third of the aorta are seen branches of a vessel arising directly from the lumen of the aorta (at arrow); proven by microscopic section. The aorta has been separated from the heart so that only part of the aortic valves is seen at the bottom. The brachiocephalic vessels are located at the right and top (with the more intense radioopacity).

*Human.* The vascularity of the ascending aorta of the adult human was comparatively less than that of the dog, but superior to that of the chicken and rabbit. The adventitia and media below atheromatous plaques of the aorta were less vascular and in fibrotic areas secondary vasa up to 30 microns in diameter were seen. Newly formed vasa of intimal origin were

observed in the outer third of the media, but no direct intimal vessels were seen. The atheromatous plaques of chickens fed cholesterol showed surrounding adventitial and medial vasa ranging from 10 to 30 microns in diameter.

*Rabbit.* The ascending portion of the aorta in the rabbit was found to be the least vascularized of all the species

examined. No direct intimal vasa vasorum were observed.

**Discussion.** This experimental study indicates that the vascularity of the ascending aorta is comparatively greatest in the dog and decreases progressively in the human, chicken, and rabbit. Although individual variations

demonstrated vascularity superior to that of the larger adult human aortas, while the aortas of premature babies generally showed better vascularization than those of rabbits and chickens of approximately similar size.

The radio-opaque mixture, found to fill the vasa vasorum 10 microns or



FIG. 2. Roentgenogram of the injected aorta (actual size) in a 45 year old woman who died postoperatively, showing the somewhat lesser vascularity of its ascending portion. No significant abnormality of the aorta was seen grossly or microscopically. The broad, well-filled coronary vessels are seen at the bottom (left and right).

occur, these results are significant since they were established after careful roentgenologic and microscopic evaluation. The species differences in number and distribution of the vasa vasorum are unrelated to the size of the aorta since the smaller dog aortas

larger in diameter, may go wherever blood flows since it has a specific viscosity of 5.40 as compared with 4.07 for blood<sup>3</sup>. The vessels filled were those of physiologic significance in that they were capable of transporting the erythrocytes with their oxygen supply.

The data obtained indicate that the blood supply through the vasa vasorum to the wall of the ascending aorta, following the vascularity, is comparatively best in the dog, less in the human and chicken, and least in the rabbit.

These basic differences in blood supply in different species may explain some of the difficulty in producing medial necrosis or arteriosclerosis in dogs and the ease with which these changes are produced in rabbits. Humans and chickens are intermediate between the extremes seen in the dog and rabbits in this tendency. It is well known that the dog is significantly less

prone to spontaneous degenerative arterial lesions than the rabbit, in which these spontaneous lesions occur frequently<sup>1</sup>. Correlating our findings with these observations it would appear that species with better vascular supply to the aortic wall have less tendency to develop these degenerative arterial lesions, while the species with poorer vascularity exhibit a greater tendency. Experimentally this supposition has received support from work in which interference with the blood supply to the aortic wall has been shown to lead to degenerative arterial lesions<sup>2</sup>. Clinically it has been noted that these lesions are less likely



FIG. 3

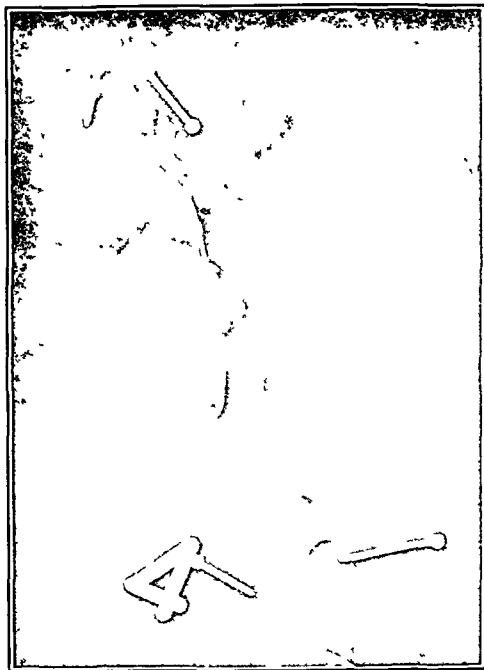


FIG. 4

FIG. 3. Roentgenogram of the aorta in the chicken after injection ( $1\frac{1}{2}$  times actual size) showing the poor vascularity of its ascending portion (the vertical part on the right). Part of the injected myocardium is still visible in the lower right corner of the specimen. The brachiocephalic vessels extend to the left at the bottom.

FIG. 4. Roentgenogram of the aorta in the rabbit after injection (actual size) showing the very poor vascularity of its ascending portion. Some of the injected myocardium has been left at the bottom of the picture. The ascending aorta extends from the upper margin of the myocardium to the mass of injection material in the brachiocephalic branches of the aorta (on the right just above the lower pin). Above this level are the arch and descending portion of the thoracic aorta.

to develop in vessels such as the pulmonary artery and peripheral veins which are well supplied by vasa vasorum.

From the preceding data a general working hypothesis can be established, namely that the development of degenerative arterial lesions appears to vary inversely with the blood supply to the arterial wall. This hypothesis does not preclude the probability that other factors, such as hormones, intrinsic cellular metabolic defects, or heredity, may play a role in the evolution of these lesions, but does emphasize the importance of the blood supply factor. Of the materials carried by the blood, oxygen would appear to be the most essential, for oxygen storage in tissue or tissue fluid is practically nonexistent<sup>5</sup>.

Conditions expected to produce degenerative arterial changes generally fall into 2 categories. In the first group are included those conditions which physiologically increase the demand for blood, and especially oxygen, by

the arterial wall without proportional increase in the supply. Such a state of affairs might be found in hypertension or even in normal physiologic growth of the aorta. In the second group are conditions actually reducing blood flow, and thereby the oxygen supply, to the arterial wall. This state might be found in syphilitic aortitis where the vasa vasorum are destroyed, or in clinical states causing prolonged anoxemia.

**Summary and Conclusions.** 1. By means of an injection technique, the vascularity of the ascending aorta in the dog, human, chicken, and rabbit was studied roentgenologically and microscopically.

2. The vascularity was comparatively greatest in the dog and was progressively less for the human, chicken, and rabbit, in that order.

3. The relationship of these differences in vascularization of the aorta to the spontaneous and experimental production of degenerative arterial lesions in these species is discussed.

We are indebted to Dr. L. N. Katz for his suggestions during this study and to Dr. O. Saphir of the Department of Pathology of this hospital and Dr. H. Popper of the Pathology Institute, Cook County Hospital and their staffs for supplying the human necropsy material.

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# PREMENSTRUAL INTOXICATION

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PREMENSTRUAL intoxication is an extremely common syndrome which, like the common cold, is often only annoying though it may be temporarily disabling. It is not a specific disease entity, but rather a cyclic recurrent impairment in health<sup>19</sup>, more often than not ignored by physicians and neglected by patients because they have come to feel that it is an unavoidable evil, an inevitable part of the distress of menstruation. The syndrome is of sufficient intensity to induce subjective symptoms lasting from 2 to 10 days premenstrually in from 40 to 50% of menstruating women. Relatively few of these patients report their premenstrual distress as primary, presenting complaints. Most commonly the symptoms are elicited only upon questioning, for like most migrainics<sup>20</sup> these patients suffer for years in silence on the assumption that because their mothers and elder sisters suffered, they too must endure this distress. When the potentiality of preventive therapy is pointed out to these young women and successful prophylaxis relieves them of their recurrent discomforts, their profound gratitude is a significant reproach of previous neglect.

As with many other disorders, the syndrome must be searched for in order to accomplish truly effective therapy. It is no longer justifiable to wait upon disablement before instituting appropriate therapy<sup>19</sup>. Only in the

more severe cases is the composite clinical picture presented. The typical syndrome is recurrent, beginning insidiously from 2 to 12 days before the onset of menstrual flow, with rising intensity of symptoms until menstruation actually starts, and then rapidly subsiding. Depression, hyperirritability, irascibility, a hair-trigger temper, insomnia, abdominal fulness, headache, nausea, vomiting, low lumbar or sacral area backache, aching in the thighs, intense hyperesthesia of the breasts, and pedal and mammary edema constitute the composite clinical picture. In the majority of cases one or another of these clinical phenomena will predominate, but occasionally patients are observed who suffer from all, or nearly all, these symptoms. In severe instances, the emotional reactions may be so violent as to border upon the psychotic. Though there is great variation in the intensity of the syndrome between different women, in any specific individual the pattern is surprisingly consistent with each recurrence. Ofttimes, anticipation of the apparently inevitable distress is a major element in adding to anxiety and, or, depression. In mild instances, merely a slight cyclic depression and ill defined restlessness may be all that occurs.

Because psychological phenomena are often more conspicuous than somatic changes, Frank<sup>5</sup> designated the

syndrome as "premenstrual tension" in 1931. There are many physicians today who feel that the whole syndrome is essentially psychogenic, an instance of psychosomatic malfunction associated with the emotional components of the menstrual cycle. This opinion is held by many psychiatrists, and especially those oriented to psychoanalysis. But there is considerable evidence, to be presented in this report, that the situation is more truly soma-psychic, and that a true chemical, though as yet unidentified, intoxication induces the psychic as well as the somatic phenomena. Machit<sup>12</sup> has demonstrated that the blood and secretions of menstruating women contain a toxic substance, poisonous to both plants and animals. This substance, which he called menotoxin, is pharmacologically related to phenanthrene derivatives, cholesterol, oxysterols, and the estrogenic sterols. It is highly probable that much of the premenstrual symptomatology is due to accumulation of menotoxin in the tissues prior to menstruation, and the rapid subsidence of symptoms associated with its release into the blood stream and thus into the urine and other secretions coincident with the onset of actual menstruation.

Habitual recurrent premenstrual hyperthermia, observed over a period of 14 years, has been reported by Reimann<sup>15</sup>. This phenomenon of fever beginning at about the time of follicle maturation and continuing until the day preceding menstruation is extremely common, but it is rarely observed unless a specific search is made. Today, the phenomenon is employed as a guide to determine the date of ovulation. As fever is associated with increased tissue hydration and a retention of bound-water, the report of Thomas<sup>24</sup> of 2 cases of massive generalized edema occurring only prior to menstruation is essentially con-

firmatory of the concept of an underlying intoxication affecting the water balance of the body. One of Thomas' patients, a woman of 38, presented a year history of premenstrual gain in weight (5 to 6 kg.), generalized edema, cephalalgia, and blurred vision. There was marked choking of the optic discs, and the spinal fluid was under increased pressure during this phase of the cycle. Recovery was invariably rapid, with a diuresis of 4,500 cc. in 24 hours. Chilling, infection, and fatigue aggravated individual attacks. A calcified lesion was discovered in the region of the pituitary gland, and the syndrome subsided when anterior-pituitary-like sex hormone was administered. The hormonal injections presumably either activated the anterior pituitary or opposed the antidiuretic activity of the posterior lobe.

Puech<sup>14</sup> presented the unusual case of premenstrual intoxication associated with renal, dermatologic, and respiratory manifestations. The patient, age 32, had had nocturnal asthma since childhood and premenstrual exacerbations of asthma since age 28. The latter appeared 4 days before the menses, subsided at their onset, and were accompanied by nasal discharge, fever, lumbar ache, and a pruritic eruption. Renal involvement was manifested by oliguria, hematuria, and the presence of granular casts. Between attacks the subject was essentially well, except for a mild asthma. Injections of progesterone during the latter half of the menstrual cycle rapidly eliminated all premenstrual signs and symptoms. The author concluded that neuro-endocrine disorders could be of fundamental importance in the pathogenesis of nephritis.

Cases similar to those cited above are rare. They are mentioned primarily to illustrate the fact that premenstrual intoxication can seriously mar otherwise enjoyable, productive lives:



Even in the usual mild case, manifested principally by minor psychic changes (particularly increased irritability), temporary loss of efficiency and difficulties in interpersonal relationships are prone to develop. Recurrent domestic discord, based in part upon the wife's premenstrual emotional vulnerability, may threaten not only her happiness but the very existence of a family unit. It would be interesting to study the correlation of premenstrual intoxication to crimes of violence committed by young women; it is quite probable that reduction of self-discipline by the intense hyperirritability so common in this syndrome may play a predisposing etiologic role.

**ETIOLOGY.** The past 20 years have witnessed the development of several theories concerning the physiologic mechanisms responsible for this syndrome. In 1930, Barath and von Magyary<sup>3</sup> reported their studies of edema during pregnancy. Some of their patients were clinically edematous; others were not. Isotonic saline solution (0.2 cc.) was injected intradermally to determine the wheal resorption time, following the technique of Aldrich and McClure<sup>2</sup>. During the last months of pregnancy, resorption time was found to be accelerated by an increase in tissue colloid affinity for water. Diminution of the blood serum albumin-globulin ratio and the swelling capacity of blood colloids was observed, even in the absence of clinical edema. These studies provoked speculation concerning the inter-relationships of ovarian activity and body water balance.

The following year, Frank<sup>5</sup> published his classical paper on premenstrual tension. He found an excess of female sex hormones in the blood when tension was at its peak. Venesection or Roentgen irradiation of the ovaries effected a lowering of circulating hormone levels and provided

symptomatic relief. One patient demonstrated a markedly elevated renal threshold for female sex hormones. Frank concluded that the premenstrual syndrome is based upon excessive production and, or, inadequate excretion of female sex hormone.

Sweeney<sup>22</sup>, discussing a phenomenon which he termed "menstrual edema", stated that it occurs to a variable degree in almost all presumably normal women. He reported that subjective symptoms were minimal and usually consisted of a peculiar tight, stuffy sensation in the abdomen, hands, and, or, feet prior to menstruation. These discomforts disappeared shortly after the period was established. Of the 42 normally menstruating women in his series, 30% gained 3 or more pounds premenstrually. Some subjects did not gain weight, but those who did noted an increased thirst, diminished urinary output, and the previously described sensations. Thorn and his associates<sup>25</sup> verified these observations in a series of 59 cases. Balance studies revealed a retention of sodium, chloride, and water during the intermenstrual and premenstrual phases and an augmented renal excretion of these substances during menstruation. Sweeney suggested that a disturbance of the sympathetic nervous system was responsible for premenstrual edema and discarded the notion of an intrinsic renal defect.

Israel<sup>11</sup> ascribed premenstrual intoxication to faulty lutenization, with consequent progesterin deficiency and a relative hyperestrogenemia. In his series of 14 cases, only 4 of the 7 whose blood and urine were assayed revealed an abnormally high renal threshold for estrogens. Since symptoms arise when corpus luteum activity should be at its height and are aggravated by the administration of estrogens, a progesterin deficiency was assumed. This theory was disputed,

however, by Provenzano<sup>13</sup>, who performed endometrial biopsies upon 15 cases of premenstrual intoxication and found a normal secretory type of endometrium in 12.

Greenhill and Freed<sup>8</sup> have expressed the opinion that sodium ion retention is partially controlled by the ovarian steroids, citing the observation that estrogens and progesterone produce sodium retention in experimental animals. The observations of Selye<sup>17</sup> that overdosage with desoxycorticosterone acetates leads to sodium retention, renal injury, and water retention are confirmatory of the idea that elevated levels of ovarian steroids premenstrually cause an accumulation of sodium ion in the various tissues of the body, which in turn produces edema. Edema, then, was considered the immediate cause of symptoms, the clinical picture depending upon the organs involved. Greisheimer *et al.*<sup>9</sup> reasoned that if the above hypothesis were correct, there should be an increase in the total base content of the serum preceding menstruation. Analyses were performed upon 13 women with premenstrual intoxication, 9 women who were free of symptoms, and 10 male students. No cyclic change in blood pH., carbon dioxide combining power, chloride, or total base were detected. The carbon dioxide content of the blood was higher in the males than in the females. Fluctuations in pH., carbon dioxide, chloride, and total base over a period of 6 weeks were greater in the males.

Obvious disagreement exists concerning the specific physiological mechanisms responsible for premenstrual intoxication. It is apparent, however, that an individual case may be based upon one or more of several dysfunctions, and that the etiologic pattern is not necessarily identical in every instance<sup>19,21</sup>. Initial symptoms may arise at the menarche, but more frequently develop during sexual ma-

turity, in the twenties or early thirties. Occasionally, the onset of symptoms is precipitated by emotional crises, often stemming from sexual frustration<sup>16</sup>. Such psychic traumata possibly evoke an excessive production of ovarian steroids, or an increased sensitivity to normal levels. Whether or not this is true, emotional disturbances are known to aggravate an already established premenstrual intoxication. Occasional cases may be based upon distinct pituitary or ovarian hormonal imbalance. Sometimes these can be detected by performing roentgenological studies of the skull, chemical studies of the blood and urine, and gynecological examinations. In our clinical experience, however, in the vast majority of instances the fundamental disturbance was simply a transitory edema and intoxication. Whether the signs and symptoms are produced by retained estrogens or by toxic metabolic products, such as the menotoxin of Macht, is as yet unsettled. Uncertainty as to the precise pathogenesis, however, should not cause therapeutic neglect when therapy is both safe and highly effective.

**THERAPY.** In general, psychotherapy alone is inadequate for the relief of premenstrual intoxication, but it is distinctly beneficial when employed in conjunction with medication. Frequently the assurance that the disorder has a truly organic (toxic) foundation will be immensely relieving to the anxious patient who has been deeply afraid that the whole matter will be laid to her being "neurotic". The realization that efforts are being made to promote relief is an additional stabilizing influence.

Frank<sup>5</sup> was among the first to recommend specific medical therapy for this disorder, employing diuretics and saline cathartics to enhance the premenstrual excretion of sex hormones. In severe cases, he resorted to Roentgen

irradiation of the ovaries to diminish estrogen production. Success with these techniques has been reported by subsequent investigators<sup>14,18</sup>. When premenstrual intoxication is incidental to an anterior pituitary deficiency, replacement therapy for the latter may stabilize water balance and eliminate premenstrual symptoms<sup>24</sup>.

Greenhill and Freed<sup>8</sup> prescribed oral ammonium chloride to decrease the retention of sodium during the last 2 weeks of the cycle, administering 0.6 gm. ammonium chloride, thrice daily. All of their 15 patients were relieved of marked premenstrual intoxication, but symptoms recurred when therapy was discontinued. Similar results with ammonium chloride and potassium chloride have been reported elsewhere<sup>13,23</sup>.

Israel<sup>11</sup> administered progestin premenstrually on the assumption that premenstrual disturbances are caused by a deficiency of this hormone and that progestin antagonizes estrogens and furthers their excretion. In stubborn cases he irradiated the pituitary to diminish the production of anti-diuretic hormone. Progestin cured 1 patient and temporarily relieved 6. Four of these 6, and 2 additional patients, were cured by low-dose Roentgen irradiation. Puech<sup>14</sup> achieved similar success with progestin, injecting 5.0 mg. 3 times the first month and 6 times the following month.

Neutralization of estrogens with parenteral and oral androgens has been strongly advocated<sup>6</sup>. The injection of 10 mg. of testosterone propionate in oil, or 20 mg. of aqueous testosterone, 1 week before the period is reported as being effective in preventing premenstrual intoxication<sup>7</sup>. Oral methyl testosterone, however, is thought to be the most effective and convenient androgenic agent for this purpose<sup>10</sup>. A daily dosage of 10 mg. for 7 to 10 days before menstruation is recommended. Androgens are rela-

tively expensive and occasionally produce disturbing side-effects, such as nausea, delayed menstruation, and almost nymphomaniac stimulation of erotic hunger. They should be employed, we feel, only in severe cases not responding to other safer and simpler therapeutic measures.

Albeaux-Fernet and Loublié<sup>1</sup> rely almost exclusively upon hormonal therapy. They reserve estradiol, which usually aggravates premenstrual symptoms, for those rare individuals with an estrogen deficiency proven by endometrial biopsy. In their experience, progesterone and testosterone usually prevent the development of the symptoms of the intoxication; hormone-resistant cases are reported to have responded favorably to weak diathermy applied over the breasts, ovaries, and pituitary.

The choice of therapy for an individual suffering from premenstrual intoxication is effected by the particular etiologic factors involved, the intensity of distressing symptoms, and the general health of the patient. Treatment should be effective, innocuous, simple, inexpensive, and free from disturbing side-effects. Certainly the simplest and most economical measures should be applied first. Of the therapeutic methods advocated, psychotherapy, diuretic medication, Roentgen irradiation and diathermy, and androgen or progesterone therapy, the first 2 approaches excel in simplicity and safety.

**Present Study.** The present study concerns 67 white women who experienced moderate to severe discomfort during the premenstrual phase of their menstrual cycle. Their ages range from 16 to 50 years, the average being 31 years. No case involving a major psychiatric disorder or endocrinopathy is included.

Fourteen (21%) of the subjects conformed to the characteristic migraine

physique<sup>20</sup>. Twelve of this number reported actual migraine headaches, and 9 regularly experienced severe premenstrual cephalalgia. The migraine constitution<sup>20</sup> may be identified readily by the following characteristics: 1, Physical: Very fine, delicate, straight hair, usually brunette; fine, transparent, child-like skin; unduly large pupils which, however, react to light and accommodation; classical, finely molded features, with narrow nostrils; cold, moist extremities; and, 2, Physiological: Decided vasomotor instability; markedly lowered resistance to fatigue; distinctly increased thermostability; and relative freedom from acute infections.

A moderately severe anemia (hemoglobin under 11.0 gm. %) was detected in 34 (51%) of the women in this study. Correction of anemia by appropriate therapy with orally administered iron, liver extract, and vitamins universally failed in relieving the premenstrual intoxication. Similarly, alleviation of intoxication did not affect an associated anemia. Simultaneous treatment of both disorders yielded good clinical results. Considering the role of the liver in both hematopoiesis and estrogen catabolism, it is possible that a hepatic defect is partially responsible for the hyperestrogenemia of some cases of premenstrual intoxication. It is likewise possible that hyperestrogenemia places an unusual burden upon the liver, and by depressing its

hematopoietic activity contributes to the genesis of the anemia.

Symptoms appeared from 4 to 10 days before the menses. They included depression, irritability, cephalalgia, engorgement of the breasts, bloating, nausea and vomiting, backache, and aching in the thighs. On the average, only 3 of these symptoms were elicited, but in some severe cases all of them occurred. The relative frequency of individual symptoms is indicated in Table 1.

In every case therapy consisted of the administration of an acid diuretic, enteric coated ammonium nitrate, for 10 days ante menses. The prescribed dosage was 1.0 gm. 3 times a day. This intermittency of administration significantly enhanced the diuretic effect<sup>4</sup>. Dietary restrictions were not imposed. Additional medication was withheld, except for antianemic nutritional supplementation when indicated, so that the clinical results could be better evaluated. Whenever ammonium nitrate therapy failed after several months' trial, alternative measures were employed.

Sixty-one (91%) of the 67 patients responded dramatically to ammonium nitrate therapy. Some symptomatic relief was usually noticed during the first month of treatment, but frequently the maximum benefits were not observed until the second or third month of therapy. In the vast majority of cases, premenstrual intoxication completely disappeared, but it tended to recur if treatment were discontinued. No particular symptom responded more rapidly or more completely than the others. There were 6 therapeutic failures, 2 of whom were aided by psychotherapy, 1 by psychotherapy with estrogen administration, and 1 by sex education. Two patients did not return for alternative treatment.

**Illustrative Cases.** CASE 1. Mrs. A. L., a 23 year old housewife, complained principally

TABLE 1. FREQUENCY OF SYMPTOMS IN PREMENSTRUAL INTOXICATION

| Symptom                | Incidence<br>% |
|------------------------|----------------|
| Emotional irritability | 68             |
| Breast engorgement     | 65             |
| Headache               | 50             |
| Backache               | 47             |
| Depression             | 36             |
| Thigh ache             | 29             |
| Bloating               | 9              |
| Weight gain            | 3              |
| Swelling of knees      | 1              |

of premenstrual hemicranic headache, preceded and accompanied by nausea and vertigo. There was no history of prodromal scotomata. Mental depression and painful engorgement of the breasts developed 5 days before the onset of each menstrual period. Physical examination revealed a typical migraine physique<sup>20</sup>, a chronic rhinitis, and congenital absence of the right arm. The erythrocyte count was 2.32 million and the hemoglobin 62%. Enteric coated ammonium nitrate, 1.0 gm. 3 times daily for 10 days ante-menses, and oral hematinics were prescribed. All premenstrual discomfort, including the migraine, was resolved, and the hemoglobin rose to 92% within 3 months.

CASE 2. Mrs. E. W., aged 33, had suffered from migraine since childhood. After the menarche attacks tended to occur premenstrually, and fatigue apparently acted as a trigger mechanism. The patient's anxieties centered about her husband, from whom she was separated, and a young son whom she was struggling to support. There was no history of mental disease, gynecological disorder, or endocrinopathy. Physical examination disclosed the characteristic migraine constitution but was otherwise negative; laboratory studies were within normal limits.

The hemicranic cephalagia was accompanied by nausea and vomiting, photophobia, and a sense of cranial constriction. Symptoms usually persisted for several days and occasionally necessitated hospitalization. Ergo-trate and barbiturates apparently hastened recovery. Observation of this patient for a period of several months indicated that her migraine developed only premenstrually. Ammonium nitrate therapy was therefore instituted. Her typical unilateral headache did not occur during the first month of treatment. Medication was omitted during the following 2 months, and her symptoms returned. Resumption of therapy and its continuance have provided complete relief, which has continued for about 8 months to date.

CASE 3. Miss M. P., aged 25, was seen initially on September 9, 1948. Her principal complaint was periodic swelling of the knees sufficiently severe to prevent her from working or performing household tasks. This condition had first developed at age 17, coinciding with the menarche. Pain, stiffness, and swelling of the right knee occurred 5 days ante menses and subsided completely by the third day following the onset of menstruation. Since June, 1948, the left knee had also been involved. Other premenstrual symptoms included fatigue, irritability, depression, backache, and bloating.

Physical examination revealed marked swelling, tenderness, and stiffness of the right knee, but no evidence of inflammation. The patellar bursae were fluctuant. The left knee was slightly swollen but otherwise apparently normal. Roentgenological studies demonstrated no osseous abnormalities. The patient's temperature was 98.6° F. and her sedimentation rate 2 mm. per hour; analyses of blood and urine were entirely within normal limits. The tentative diagnosis was premenstrual intoxication manifested principally by intermittent hyarthrosis. Ammonium nitrate therapy was started, and during the ensuing three months premenstrual signs and symptoms have become progressively less severe. Both knees continue to swell slightly immediately before the period, but this no longer interferes with her work. At the present time it is impossible to predict how permanent or complete her recovery will be.

Summary. The syndrome of premenstrual intoxication has been described and various theories regarding its etiology have been discussed. Past and current therapeutic methods have been evaluated. A series of 67 cases treated with enteric coated ammonium nitrate, 1.0 gm. 3 times a day for approximately 10 days premenstrually, has been presented. Sixty-one (91%) of the patients included in this study responded with dramatic improvement, and almost complete prophylactic control of their symptoms. Improvement was noticeable during the first month of therapy and usually reached a maximum after 2 or 3 months. Symptoms tended to recur upon discontinuance of therapy. The diuretic therapy was much less effective if applied *after* the onset of symptoms of intoxication, as observed in those patients who were too forgetful to start their medication in advance of each recurrent episode. In those instances where menstruation was irregular, administration of the ammonium nitrate was prescribed to start 10 days before the expected date of the next period assuming the shortest cycle for the particular patient, and then continued until menstruation actually started.

Thus, the duration of actual administration might vary from 8 or 9 to as much as 25 days. A liberal fluid intake, to enhance diuresis, was always encouraged. Many of these patients had previously consumed very little water habitually.

It is believed that premenstrual intoxication, with its attendant edema and retention of sodium chloride and toxic materials is engendered by either some cyclic appearing metabolic toxins such as the menotoxin of Macht, or a transient hyperestrogenemia or both. The high frequency of coincident nutritional anemia and migraine is sug-

gestive of some underlying constitutional factor as yet not clearly oriented. The remarkable prophylactic abatement of symptoms, including the psychic aberrations, by safe and simple diuresis induced by the acid diuretic salt, ammonium nitrate, is strongly supportive of the concept that the basic factor in this symptom complex is an intoxication. The nitrate rather than the chloride salt of ammonium is employed because of its greater diuretic efficiency, and the avoidance of increasing the chloride content of the tissues<sup>21</sup>.

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# PARATHYROTOXICOSIS: THE SYNDROME OF ACUTE HYPERPARATHYROIDISM

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HYPERPARATHYROIDISM is practically always thought to be a chronic disease. This misconception may be excused perhaps because we still know very little about the "newest" of the endocrine glands. They were first differentiated as non-thyroid tissue only 70 years ago<sup>27</sup>; the first successful removal of an adenoma with improvement of a patient with osteitis fibrosa cystica occurred only 23 years ago<sup>13</sup>; and the name "hyperparathyroidism" itself is only 20 years old<sup>14</sup>.

At first it was considered as primarily a disease of bone. Later the high incidence of renal stones was noted, and only recently have the clinical features of neuromuscular and digestive disturbances been emphasized. The usual duration before recognition is perhaps 3 to 20 years or more.

But hyperparathyroidism can also be an acute and often fatal disease. In this respect it resembles its next-door neighbor, the thyroid gland, and perhaps the not-so-euphonious word "parathyrotoxicosis" is appropriate.

Only a few cases of acute parathormone intoxication have been described, but their signs and symptoms are rather characteristic, and it is the purpose of this paper to describe the short and severe syndrome of parathyroid "intoxication".

EXPERIMENTAL PARATHORMONE OVERDOSAGE. Experimental parathyroid

poisoning produces another distinctive picture. Collip<sup>8</sup> injected his preparation of parathormone into dogs and produced vomiting, diarrhea, and marked muscular atony. The serum calcium levels rose to about 20 mg. per 100 cc. but fell somewhat, terminally. The serum phosphorus and non-protein nitrogen rose shortly before death. There was marked dehydration and hemoconcentration.

Post-mortem studies, in this and other reports<sup>7</sup>, revealed an increased calcium content in the kidney, gastric mucosa, myocardium and lungs. At times a hemorrhagic gastritis was found. Hueper<sup>16</sup> emphasized the frequency and extent of intravascular thromboses. Some of the other features which were often noted were fever, bradycardia, terminal acidosis (unless there was excessive vomiting), and decalcification of bone with a hyperemic marrow.

The definitive work of Cantarow, Stewart and Housel<sup>6</sup> firmly established the pathological changes in dogs following administration of parathyroid extract. Short term experiments, 72 hours, again showed the widespread calcification already described. But, if anything, there was an inverse relation between the extent of the damage and the serum calcium and protein levels. These authors believe that the degenerative changes were due to a direct toxic effect of the excess hormone.

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Shelling<sup>28</sup> showed that the most conspicuous effects of parathyroid extract administration is the loss of water and electrolytes. The terminal results of dehydration, hypochloremia, hyperphosphatemia, retention of nitrogenous products, anuria, uremia and death being those of salt and water imbalance. He believes that the entire symptomatology of "parathyroid poisoning" except for the hypercalcemia can be produced by forced diuresis, and he suggests that the infrequency of these symptoms in patients with hyperfunctioning parathyroids may be explained by their unrestricted intake of food, salt and water.

**PUBLISHED CASES.** There is a striking similarity between these experimental findings and certain clinical reports.

Oliver<sup>23</sup> reported 2 cases of fatal acute hyperparathyroidism. Both were women in the sixth decade of life. Both had anorexia, vomiting, constipation, weakness and lassitude, with increasing drowsiness, a slight fever, tachycardia, dehydration and both terminally showed impaired renal function without hypertension. Post-mortem calcium determinations were 17.4 and 19.6 mg. per 100 cc. Both had marked nitrogen retention in the blood. Furthermore, both patients were found to have a chief cell adenoma of the parathyroid gland on autopsy. Severe tubular necrosis and moderate glomerular necrosis was found. Calcium was deposited in varying intensity in the myocardium, the internal elastic laminae of the coronary arteries, the renal tubules and glomeruli, the lungs, stomach wall and in the blood vessels generally. No organs, in either case, were said to show enough abnormality to have caused death.

Similar patients have been described by Smith and Cooke<sup>29</sup>, Hanes<sup>4</sup>, Mellgren<sup>21</sup>, Arnold<sup>2</sup>, Herzenberg<sup>5</sup>, Morrelle<sup>22</sup>, and Young and Halbert<sup>32</sup>. Vom-

iting, constipation, and marked weakness and lassitude were common to all. Epigastric or generalized abdominal pain and tachycardia were usually noted. Hypercalcemia and nitrogen retention were present in all patients in which such determinations were made. In one<sup>27</sup>, the serum phosphorus was 4.8 mg. per 100 cc., in another<sup>22</sup>, 1.8 mg. (This latter report resembles our Case 1). An adenoma of the chief cell variety was found in all but 2; one of the latter<sup>14</sup> showed a "cystic and partly calcified and necrotic tumor", the other<sup>21</sup> was reported as being composed of *wasserhelle* cells.

Widespread calcinosis was found; in all of these cases the kidney suffered especially, tubular necrosis as well as glomerular damage being common. Interstitial calcification was present in the myocardium of 6 of the 10 patients and to a lesser extent in the lungs, stomach and liver, while evidence of osteitis fibrosa cystica was noted in 4 of these reports.

Rogers<sup>25,26</sup> reported 3 instances of acute primary hyperparathyroidism associated with duodenal ulcer. Treatment by diet and alkali seemed to aggravate the symptoms of vomiting and epigastric pain. Terminally azotemia and lethargy were prominent. No calcium or phosphorus determinations were made as the diagnosis was not suspected ante-mortem. Primary hypertrophy and hyperplasia of the parathyroid was noted in two. Nephrocalcinosis and generalized metastatic calcification was found.

Other cases also had a duodenal ulcer-like clinical picture, *i.e.*, a patient with a history of "peptic ulcer" but *no* free hydrochloric acid<sup>9</sup>; a case with healed duodenal ulcer on autopsy<sup>10</sup>; a patient who had healed gastric ulcer on Roentgen-ray but achlorhydria and made worse by ulcer therapy<sup>15</sup>; a patient with low gastric



acidity epigastric pain and vomiting with return of free hydrochloric acid after parathyroidectomy<sup>22</sup>.

Of the 5 cases herein reported, Case 4 had a deformed duodenal bulb with signs and symptoms of duodenal ulcer; all had had gastrointestinal symptoms.

Acute hyperparathyroidism has recently been described in association with carcinoma of the gland<sup>31</sup>. The symptoms here too were persistent nausea and vomiting. Marked hypercalcemia but essentially normophosphatemia was present. There was impaired renal function and moderate azotemia; no casts were seen in the urine. The authors felt that the cause of death in this case could not be ascribed to renal damage or excessive loss of base. At any rate, they made the interesting suggestion that hypercalcemia may have increased cardiac muscle irritability, to the point of ventricular fibrillation, and that administration of large amounts of sodium (to combat acidosis) may have led to a washing out of potassium thereby removing an inhibitor of cardiac irritability.

**Case Reports.** *CASE 1. J. K. Simple Primary Hyperparathyroidism, acute clinical course.* A 30 year old colored man was admitted to the medical service of Dr. D. N. Kremer at the Philadelphia General Hospital on September 27, 1947, for a pain in the abdomen which began for the first time on the day of admission. He had been previously completely well and had never seen a doctor before this episode. The sharp, brief pain originated in the umbilicus and radiated to the left costovertebral angle. Shortly afterward, he began to vomit and was brought unconscious to the hospital.

On examination he was a well developed intelligent man not visibly ill. His blood pressure was 112/70 mm. Hg., pulse 76. The teeth were in excellent condition. No physical abnormalities at all were noted. He suffered a recurrence of the severe periumbilical pain and vomiting on the second and fourth hospital day. He also began to complain of weakness, fatigue and anorexia. The following laboratory examinations were within normal limits: urine analysis, blood sugar, urea, albumin, globulin, white blood cell count,

bilirubin, sickle cell preparation, cholesterol and spinal fluid, Bence-Jones protein, intravenous urogram and red cell fragility. The blood Kline test was 3+, 64 Kahn units.

On October 24, 1947, he accidentally fell on the ward and sustained an avulsion fracture of the patella with hemarthrosis. In addition to anemia, he was found to have hypercalcemia (17.5 mg. per 100 cc.) and hypophosphatemia (1.8 mg.) but no hypercalcuria was present. Roentgen studies of the skeleton revealed increased sclerosis and trabeculation.

On November 24, 1947, 2 small parathyroid glands about 1 cm. in diameter were found and removed. Histologically, it was described (Dr. Wm. Ehrlich) as a grey-pink well-encapsulated adenoma (6 x 5 x 3 mm.) showing no "clear" cells, or mitotic figures. Biopsy of the ilium revealed osteitis fibrosa cystica.

The serum calcium level had not fallen as late as the 18th postoperative day, nor had the serum phosphorus risen to normal levels. The Sulkowitch test was strongly positive 12 days after operation, showing that unfortunately the metabolic disorder was not relieved.

**CASE SUMMARY.** A young man, previously entirely asymptomatic, suddenly developed severe abdominal pain and vomiting, followed by weakness and lethargy. Following a fracture on the ward, he was found to have hyperparathyroidism, with osteitis fibrosa cystica. Removal of a small adenoma caused no change in electrolyte pattern.

The extremely rapid onset of symptoms suggest that his calcium level may have suddenly reached "toxic" levels, because from the bone changes the disease must have been present for some time.

*CASE 2. F. K. Severe renal insufficiency, with "acute" secondary hyperparathyroidism, "renal rickets".* A 34 year old white woman first entered the medical clinic of the Philadelphia General Hospital on March 25, 1946, for amenorrhea and bilateral ankle edema. Examination revealed moderate cardiac enlargement with an apical systolic murmur and a moderate degree of pitting edema and tenderness of the legs. The reflexes were hyperactive. Roentgen-ray examination of the heart and lungs, an electrocardiogram and basal metabolism test were normal as were the blood sugar, serologic test and serum albumin and globulin. She was profoundly anemic. The urine revealed a 3+ albumin reaction with a specific gravity of 1.007 and the blood urea nitrogen was 155 mg. per 100 cc.

She was admitted to the hospital (Service

of Dr. D. N. Kremer) on April 15, 1946, with thrombophlebitis of both legs. The past history was irrelevant.

She appeared moderately dehydrated but otherwise normal. The blood pressure was 138/88 mm. Hg., and a sinus tachycardia was present.

Laboratory examinations revealed a persistent moderate albuminuria (3.2 gm. per liter in one determination) and a maximum specific gravity of 1.008 (1.005 on a Fishberg concentration test). In spite of this, no red cells or casts were seen. A 12 hour Addis count revealed a specific gravity of 1.004 and the leukocytes were too low to count. She was found to have azotemia (blood urea nitrogen of from 40 to 240 mg. per 100 cc.),

The patient was discharged June 4, 1946, only to return 20 days later because of persistent vomiting, diarrhea and melena, and diffuse abdominal pain. She was thin, pale and listless. Her face appeared puffy and there was moderate ankle edema. The blood pressure was within normal limits, and a long rough systolic murmur was heard at the apex. The abdomen was normal. She received parenteral fluids without much change in her condition until July 4, 1946, when again she had severe abdominal postprandial pain. She became restless in spite of morphine and in her struggling fractured her left radius and ulna. Roentgen-ray films of the fractured arm revealed marked calcification of blood vessels. Until she died 4 days later, her abdomen was



FIG. 1. Calcified area in myocardium. (Case 2.)

acidosis ( $\text{CO}_2$  from 8.6 to 20.3 [usually 9 to 12] m. eq. per liter), hypochloremia (chloride 92.8 to 100 [usually about 94] m. eq. per liter), and hyperphosphatemia (8.4 mg. %). The blood uric acid was 6.0 mg.

The determination for sugar, albumin, globulin, cholesterol, Bence-Jones protein and urine culture were normal. Achlorhydria after histamine was found. An ophthalmological consultant reported that 3 or 4 small flame-shaped hemorrhages were seen but no exudates or other abnormalities. "The fundus changes could probably be secondary to the severe anemia."

markedly distended and extremely tender and rigid.

Laboratory findings included extreme anemia (hemoglobin between 2.8 and 3.1 gm. per 100 cc.) acidosis ( $\text{CO}_2$  from 15.8 to 8.6 m. eq. per liter terminally) with no hyperpnea observed, and uremia (urea nitrogen from 90 to 208 mg. per 100 cc. terminally). The plasma proteins were normal. Just before death the serum calcium was 6.4 mg. and the serum phosphorus 11.3 mg. In the urine no casts or red cells were seen, although she had a moderate albuminuria.

*Autopsy.* Gross (pertinent findings only).

Aorta: mild calcification of lower abdominal portion; heart: calcification of myocardium (Fig. 1) coronary vessels and endocardial surface of left auricle, calcific deposits of mitral valve; calcification of tongue arteries (Fig. 2); spleen: calcified infarction, calcification of vessels entering hilus, bilateral pyelonephritis with scarring and atrophy of left kidney, calcification; multiple jejunal infarcts with necrosis and gas bacillus infection; acute parenchymatous degeneration of liver. Hyperplasia of parathyroid.

to prolonged renal insufficiency with acidosis and secondary hyperparathyroidism. The latter condition probably existed in an acute severe form.

In another hospital, 3 cases were observed which may be considered as modified variations of the syndrome.

CASE 3. F. Z. K. *Parathyroid adenoma. Renal insufficiency secondary to hyperparathyroidism.* This patient was 44 years old at the time of his first admission to the hospital in 1935. Four years before admission he devel-



FIG. 2. Calcification of arteries of tongue (Case 2.)

*Microscopic.* Heart: patches of interstitial calcification (Fig. 1), metastatic calcification of arteries; kidney: old glomerulonephritis and pyelonephritis and interstitial calcification; fatty dystrophy and autolysis of liver; diffuse peritonitis; hyperplasia of parathyroids; brain: multiple areas of necrobiosis, chronic passive congestion, no calcification.

CASE SUMMARY. A case of adult "renal rickets (?)" in which chronic nephritis led

opened severe pain in both sacral-iliac regions, together with epigastric pain and frequent vomiting. Three years later severe cramps in both calves and later in the abdominal and arm muscles were noted. Eight months before this admission all symptoms became marked.

Physical examination revealed an acutely ill, prostrated white man. No glands were palpable in the neck. There was moderate thickening of the peripheral vessels, occa-

sional muscle twitches and exaggerated normal reflexes.

Laboratory studies showed a moderate anemia, a non-protein nitrogen between 50 and 90 mg. per 100 cc., serum calcium 19.3 mg. and serum inorganic phosphorus 4.3 mg. Other blood chemical determinations were normal. The phenolsulphthalein excretion was impaired, 15 to 20% in 2 hours. His urine showed 3 to 4+ albumin, a rare red blood cell and a small number of hyaline casts. Roentgen examination of the gastrointestinal tract showed a persistent duodenal deformity. But the patient had achlorhydria even to histamine. Roentgen examination of the kidneys revealed a group of calcified bodies in the region of the left kidney. There was some osteoporosis of the tibia and forearm bones. The skull was normal.

A diagnosis of hyperparathyroidism was made. Surgical exploration revealed the presence of an adenoma in 1 of the 2 glands felt on the right side. There was another small questionable nodule felt on the left side. This was not removed. The pathological report was that the cells were "wasserhelle" in type, having "arisen entirely from the chief cells".

He had a smooth postoperative course. The calcium level fell to 8.6 mg. and the phosphorus which, significantly, was somewhat raised in spite of a greatly elevated calcium, fell to normal levels (3.1 mg.).

Four months later he had a recurrence of epigastric leg pains. Chemical determination of the blood and urine analyses were essentially normal. Five years after operation, nausea, vomiting, headaches and weakness developed. Dyspnea became more marked and he had suffered an episode of severe substernal pain radiating to the back and abdomen one month before admission.

The blood pressure was 222/158 mm. Hg., calcium 9.8 mg., phosphorus 5.3 mg., non-protein nitrogen 66 mg. The  $\text{CO}_2$  combining power was 46.6 vol. % and serum sodium was 144 m. eq. per liter, casts, albumin and occasional red and white blood cells were found in the urine. The phenolsulphthalein output was 10% in 2 hours. He died shortly after another attack of severe chest pain.

**Autopsy.** 1. Foci of atrophy, scarring and calcification in kidneys. Foci of calcification in sclerae of eyes and alveolar walls of lungs. 2. Dissecting aneurysm of aorta and right main renal artery. Organizing thrombi in aneurysm with stenosis of right renal artery. Rupture of aneurysm into left pleural cavity. 3. Marked sclerosis of small branches of

coronary arteries, intrarenal arteries and arterioles. Necrosis of central liver cells. The vertebral marrow was essentially normal. The remaining parathyroid tissue was histologically normal.

**CASE SUMMARY.** A 44 year old man who had a two-year history of abdominal pains, vomiting and muscle cramps, elevated serum calcium and normal phosphorus. Removal of a parathyroid adenoma cured his chemical imbalance, but only temporarily relieved his symptoms. Five years later, suffering from hypertension and renal insufficiency, he developed an aortic aneurysm which dissected and ruptured into the pleural cavity. Autopsy revealed calcification in the kidneys and lungs.

The patient probably had "acute" hyperparathyroidism due to an adenoma of the gland, removal of which cured the parathyroid dysfunction. Renal insufficiency, secondary to hyperparathyroidism, was partially relieved by the operation, but eventually led to severe hypertension.

**CASE 4. I. S. Probably very early acute hyperparathyroidism.** Sarcoidosis. The patient was a 34 year old colored man who developed uveoparotid fever 6 years before his final admission in 1940. Two brothers also had sarcoidosis. In 1937 he had roentgenographic evidence of pulmonary and osseous sarcoidosis, which was confirmed by biopsy of a skin nodule. For one year before admission he had occasional episodes of vomiting, epigastric fullness after meals and constipation. For one month preceding admission he noted nocturia, polyuria and polydipsia.

Physical examination showed a well developed young man. The spleen and liver were enlarged, and there were multiple skin nodules. The blood pressure was 130/90 mm. Hg.

There was no anemia. The white cell count was normal, with a 7% eosinophilia. The urine was acid, specific gravity of 1.018, no albumin, occasional hyaline casts, and a moderate microscopic hematuria. The serum NPN was 44 mg. per 100 cc., total protein 7.6 gm., albumin 3.37 and globulin 4.23 gm. The  $\text{CO}_2$  combining power was 71.1 vol. %. The PSP excretion was 78% in 2 hours.

While on the wards he began to complain of rather vague abdominal pains, especially after meals. There was some nausea but no vomiting. Roentgen-ray examination of the gastrointestinal tract showed a hyperactive stomach with a duodenal bulb which was deformed and which suggested an ulcer. A small calcified body was seen near the lower pole of the left kidney.

He was started on the orthodox Sippy

regimen on December 15, 1940. Three days later the epigastric distress was somewhat relieved. On December 24th he rather quickly became disoriented, incoherent, weak and mentally dull. His blood pressure was 100/70 mm. Hg. He soon developed Cheyne-Stokes respirations and became stuporous. The clinical impression was an acute alkalosis, perhaps due to the milk and alkali intake. In spite of attempts to improve his electrolyte disturbance, he died on December 27th.

Blood chemical determinations on the day of death were as follows: NPN 108 mg. per 100 cc., chloride 83 m. eq. per liter,  $\text{CO}_2$  combining power 80.5 and later 106 vol. %. Sodium 138.5 and potassium 5.0 m. eq. per liter. The total protein was 6.76 gm. with an albumin of 2.77 gm. Calcium 16.5 and phosphorus 9.9 mg. In short, hypercalcemia plus hyperphosphatemia, hypochloremia, alkalosis, retention of nitrogen and reduction in sodium were present.

*Autopsy.* 1. Sarcoidosis 2. Bilateral renal calculi 3. Calcium deposits in renal tubules 4. Tuberculosis of axillary nodes with sinus tract. The parathyroids were slightly enlarged but normal microscopically.

**CASE SUMMARY.** A 34 year old man with widespread sarcoidosis suddenly developed acute alkalosis while on a Sippy diet. There was evidence of acute renal insufficiency with retention of nitrogenous products. Terminally, he had hypercalcemia with hyperphosphatemia. The parathyroids were enlarged. Microscopic study of the kidneys revealed calcification of the tubules, many of which were apparently occluded by the calcified material. There was also marked cloudy swelling with large colloid droplets in convoluted tubules. The relation of alkalosis and renal calcification is discussed below.

**CASE 5. M. L. Acute hyperparathyroidism secondary to glomerulonephritis.** This 24 year old white man complained of headache and pains in the back when admitted in December, 1930. About 9 months before admission he developed nocturia and polyuria, but no dysuria or hematuria. Severe frontal and occipital headaches were present for 4 months, and severe vomiting, weakness and anorexia soon followed.

Physical examination revealed a pale, thin young man. The blood pressure was 145/75 on admission and never rose above this figure. In spite of a PSP excretion of O, a NPN of 186 mg. per 100 cc., a marked albuminuria and fixed specific gravity of the urine, there were no casts, a rare red and white blood cell in the centrifuged urine specimen, and no exudates or hemorrhages in the eyegrounds. This was a most unexpected finding.

His course in the hospital was progressive and downhill. His anemia became worse, the NPN rose to 312 mg. Creatinine was 13.2 mg., the  $\text{CO}_2$  combining power varied from 25 to 35 vol. %. His symptoms were nausea, "burning" in the stomach, anorexia, epistaxis and gradually intractable vomiting. He excreted over 2 gm. of albumin per liter of urine, and only very rare red cells and casts. Fifteen urine examinations always showed a neutral or acid reaction. There was no hyperpnea with a  $\text{CO}_2$  around 25 vol. %. Terminally the serum calcium was found to be 11 mg., the uric acid was 11.6 mg. and sodium chloride was 414 mg.

*Autopsy.* 1. Bilateral parathyroid tumor nodules. 2. Extensive calcification of alveolar walls, bronchioles and venules of the lungs. 3. Extreme chronic nephritis with calcification of the tubules. 4. Lobular pneumonia. There was practically no arteriosclerosis.

Both kidneys together weighed 80 gm., were pale and finely granular. There was practically no cortex seen. The changes in the vessels of the kidneys were fairly marked but extremely irregular in extent and character, and "it is difficult to find hyaline arterioles which might account well for the glomerular changes, there were hyalinization and thickening of the capsules." The vertebral bones were rarified and numerous large osteoclasts were present. No calcification was found in the stomach. The skull was not examined. In the parathyroid tissue no fat was seen. The chief cell was predominant but some cells were clear and tended toward the "wasserhelle" variety.

**CASE SUMMARY.** A young man developed progressive and extreme renal insufficiency and died in uremia. Gastrointestinal symptoms were prominent. The expected urinary and retinal findings were conspicuously absent. On autopsy he was found to have enlarged parathyroid glands and extensive calcification of lung and kidney. This is regarded as a probable case of secondary hyperparathyroidism, but with acute manifestations.

**Discussion. Clinical Picture of Parathyrotoxicosis:** From the existing literature we can construct a "classical" case of acute hyperparathyroidism. A middle-aged man or woman who may have had a previous history of gastrointestinal disturbances rather quickly develops epigastric pains, persistent vomiting and constipation. Weakness and apathy are marked. Weight loss is present if the symptoms last long

enough. Probably the clinical impression will be that of a duodenal ulcer, but even though a duodenal deformity may be present, achlorhydria is as likely to be present as not. In spite, or perhaps because, of an ulcer regimen, the course is progressive. Terminal fever and azotemia occur. The blood pressure often ranges from upper normal to frank hypertension. A moderate albuminuria usually with few, if any, casts or red cells will be found. The serum calcium will be markedly elevated in the primary type, but the serum inorganic phosphorus may be normal or elevated. Roentgen-ray examination of the kidneys may show a diffuse mottled calcification. On autopsy there are likely to be calcium deposits in the renal tubules (nephrocalcinosis) as well as in the gastric mucosa, alveolar tissue, myocardium and elsewhere. Frequently an adenoma of the parathyroid gland is found, but other cases may show a diffuse hyperplasia (both primary and secondary varieties).

These signs and symptoms may be due to hypercalcemia *per se*. (Case F. K., of course, had hypocalcemia and hyperphosphatemia). Hypervitaminosis D with hypercalcemia may also lead to nausea, vomiting, anorexia, epigastric pain, weakness and constipation. Gutman *et al.*<sup>11</sup> drew attention to the occasional predominance of gastrointestinal symptoms in hyperparathyroidism and ascribed them to the "toxic" manifestation of the hormone. However, Shelling<sup>28</sup>, as was mentioned, has ascribed the symptomatology to the marked loss of water and electrolytes which often occurs.

Clinically, when gastrointestinal symptoms predominate, the diagnosis

may be suspected when a patient with a "duodenal ulcer" shows intractable vomiting in the absence of pylorospasm or gastric retention, when the vomiting and epigastric pain is aggravated by a high calcium, high phosphorus and, or, alkali intake (the basis of our commonly used ulcer treatments), when there is marked muscle weakness and lethargy, and when there is terminal uremia with polyuria and polydipsia. The presence of hypercalcemia and azotemia without acidosis is strongly suggestive of acute hyperparathyroidism. A review of the reported cases shows 2 outstanding clues to this disease: the presence of an *atypical* "duodenal ulcer", and uremia *without* casts or marked acidosis.

It is difficult to assay the role of the calcium-phosphorus intake in acute parathyroid intoxication. About half the cases in the literature received a high milk diet for their gastric symptoms, and a number presumably received also, alkali which (as will be shown) may be an important factor in renal calcinosis. It can be theoretically assumed that when there is a sudden excessive outpouring of parathyroid hormone with a calcium diuresis, and an excess amount of calcium is given, there is further polyuria, dehydration and electrolyte loss (Shelling). If alkali is added, there is a greater likelihood of precipitation of calcium in the renal tubules. Both phenomena may lead to nitrogen retention and renal insufficiency. The amount of phosphorus in the blood rises, as it does in uremia from any cause, and we find the curious picture of an elevated calcium *and* phosphorus.\*

\* After this paper was submitted for publication, Burnett, Commons, Albright and Howard (New England J. Med., 240, 787, 1949) described 6 patients with a peptic ulcer syndrome who received excessive milk and alkali for years. Hypercalcemia without hypercalcuria or hypophosphatemia, renal insufficiency, alkalosis and calcinosis were found. They did not believe this picture was due to primary hyperparathyroidism, and ascribed the findings to: a, excessive milk and alkali intake; b, kidney damage; and c, hypercalcemia.

Ellsworth and Fitcher<sup>9</sup> showed that in nephrectomized dogs, injection of parathyroid extract causes hypercalcemia without a fall in organic phosphorus, or even a slight rise, and Goadby and Stacey<sup>20</sup> found that in patients with renal insufficiency, parathyroid extract fails to produce the "phosphate diuresis" found in normals. Thus, it might seem that renal insufficiency is the prerequisite for the development of the hyperphosphatemia found when hyperparathyroidism is associated with renal disease.

and alkali is seriously detrimental to the patient with acute hyperparathyroidism.

The renal disease of primary parathyrotoxicosis is most peculiar. In most cases in the literature, there was much less histological damage in the kidneys than might be expected from the retention of nitrogenous products. Furthermore, the urine rarely shows more than a rare red or white blood cell and infrequent casts. Albuminuria, if present, is usually slight. It would seem that there is a minimal degree

TABLE I.—COMPARISON OF ACUTE AND CHRONIC HYPERPARATHYROIDISM

|                          | <i>Acute</i>  | <i>Chronic</i>   |
|--------------------------|---|--|
| Duration                 | Under 1 year, often under 6 months  | 3 to 20 years or more  |
| Serum Calcium            | Elevated  | Elevated   |
| Serum Phosphorus         | Normal or elevated  | Low  |
| Gastro intestinal system | Intractable vomiting, epigastric pain, constipation, occ. duodenal ulcer, and gastric mucosa calcification. | Constipation, symptoms usually slight                                    |
| Bone                     | Normal, some changes in prolonged cases.  | Frequent osteitis fibrosa cystica, generalized.                          |
| Kidney                   | Tubular calcification, uremia, normal or minor urine changes, no acidosis                                   | Calculi in $\frac{1}{4}$ of cases, polyuria, hypercalcuria, uremia rare. |
| Muscular system          | Marked lassitude, weakness, lethargy.   | Hyporeflexia frequent.   |
| Myocardium               | Food calcification.   | Normal   |
| Lungs                    | Microscopic calcinosis.   | Normal   |
| Parathyroid glands       | Primary adenoma or hyperplasia secondary to renal disease.  | Same   |
| Prognosis                | Poor.   | Fair, depends on early recognition.                                      |

We do not know which condition began first in Case 3. We believe that renal disease was primary in Cases 2 and 5, but there is no evidence for any significant preceding renal disease in Cases 1 and 4. Microscopic hematuria and polyuria had been noted in Case 4 before the development of clinical hyperparathyroidism, but various renal function tests were normal.

From the evidence in Case 4 particularly, and from others<sup>25,26</sup> it would seem that the administration of calcium

of increased glomerular and tubular permeability, but rather a reduction in the clearance of urea, phosphorus and other substances. Curious, too, is the frequent absence of acidosis although in Case 4 the inorganic alkaline powders of the Sippy treatment, could be the explanation.

In Table I we have compared the acute and chronic types of hyperparathyroidism. It appears that when calcium is withdrawn slowly from its body stores (chiefly bones) and

excreted in large amounts in the urine, the intake of calcium to a large extent determines the type of clinical picture. With a prolonged negative calcium balance osteoporosis and osteitis fibrosa may result. With a small negative calcium balance, resulting from a high calcium intake, the bones are less porous but the hypercalcuria leads to renal calculi, with its complications and sequelae.

These 2 major types have a gradual onset, prolonged course and are not necessarily severely disabling. This is in marked contrast to the rapid onset, short course and severe symptoms seen in the type appropriately called "acute".

There is undoubtedly a wide variety of forms of the acute stage, as there is in the chronic stage. We believe Case 1 (J.K.) represents a simple form of acute hyperthyroidism, whose symptomatic course was extremely brief. We believe Case 3 (F.Z.K.) had acute primary hyperparathyroidism, the course of which was aborted by surgery; Case 4 (I.S.) suddenly developed the clinical picture of acute hyperparathyroidism and died in alkalosis; Cases 2 and 5 (F.K. and M.L.) died in uremia probably due to chronic glomerulo-nephritis but had the clinical and pathological evidences of parathyroid intoxication and thus may be considered as cases of acute secondary hyperparathyroidism; parathyroid hyperplasia, of course, is occasionally found with chronic renal disease<sup>24</sup>.

*Histological Picture of Parathyrotoxicosis:* Since all the reported cases showed a rather widespread calcium deposition in the tissues of the body, particularly in the kidneys, it is necessary to evaluate this finding as a characteristic of the syndrome. This subject has been ably reviewed by Vaughan, Sosman and Kinney<sup>30</sup>.

Pathological calcification may result

from an abnormally high concentration of calcium or phosphate in the blood with precipitation of the salt in the tissues, or it may result from local tissue damage with calcinosis in the presence of normal serum levels. The areas of predilection are areas where there are marked changes in the pH of the media or increased phosphatase concentration<sup>30</sup> or, as Martz<sup>20</sup> has claimed, in organs where acid is excreted into a cavity (lungs, stomach, kidney). It is suggested that the loss of acid leaves the intracellular fluids correspondingly alkaline. Calcium saturation in the presence of alkalosis leads to calcium precipitation. However, in cases of massive alkali therapy reported by Kirsner *et al.*<sup>17</sup> calcium was deposited in the renal tubules although the urine was not acid. Hypochloremia seemed to be an important factor according to these authors. Our case of acute alkalosis (Case 3, I.S.) also had hypochloremia. It should be mentioned, however, that the opposite findings, nephrocalcinosis with hyperchloremia and acidosis, have been reported<sup>1,3,5,12</sup>.

Whereas the renal tubules may show calcification from a wide variety of causes (tuberculosis, mercury and sulfonamide poisoning, for example), the picture of pathological calcification in the lungs, stomach, myocardium and elsewhere, strongly suggests an origin like that in animals<sup>6,7,8,16</sup> that have been given huge doses of parathyroid hormone. It seems logical then to ascribe the diffuse calcinosis seen in hyperparathyroidism, as in vitamin D poisoning, to the marked hypercalcemia which leads to supersaturation and precipitation of calcium salts. Probably the loss of water and electrolytes, particularly chlorides, aggravate the mechanism.

It might be argued that the histological appearance of the parathyroids in Case 2 (I.S.) rules out hyper-



parathyroidism. There are reports in the literature of very little, if any, change in cytology of the parathyroid glands in the presence of clinically obvious over-functioning of the gland<sup>4,13,28</sup>. One patient, for example, (A.W.) (seen at another hospital) with large renal calculi and osteoporosis, had a pre-operative serum calcium of 11.8 mg. per 100 cc. and phosphorus 2.3 mg. Removal of a moderately enlarged parathyroid gland, which was completely normal histologically, led to a rapid fall in calcium to 5.6 mg. and tetany. The serum inorganic phosphorus rose to somewhat elevated levels. When discharged, one month after operation, the serum calcium was 7.1 mg., phosphorus 5.0 mg. One could scarcely question the diagnosis of hyperparathyroidism clinically, and yet the gland proved to be microscopically normal in every respect.

**Summary.** Five cases of the acute phase of hyperparathyroidism have been presented. Three might be regarded as "primary"; 1 died in the early stage, 1 had the gland removed but not until irreversible renal damage occurred, and the 3rd had a parathyroidectomy before renal damage occurred. The other 2 may be taken

to be "secondary" to advanced nephritis.

The diagnosis should be kept in mind when one sees a patient with a short, relatively stormy course, of predominantly gastrointestinal symptoms suggesting an atypical peptic ulcer. In addition to hypercalcemia, a normal or elevated phosphorus will be found in the primary form. Renal insufficiency with terminal uremia (yet with insignificant microscopic findings) and little, if any, acidosis can develop terminally; operative removal of the glands may forestall the progressive course. Calcification of lungs, stomach, myocardium and arteries, but particularly the renal tubules will be found at autopsy.

Either primary or secondary hyperparathyroidism may be acute in onset or may develop an acute exacerbation.

The clinical and pathological picture closely resembles parathyroid intoxication of the experimental animal. A review of the literature shows that this syndrome is a definite entity. The acute form of parathyroid hormone intoxication, "parathyrotoxicosis", should be recognized early because only surgical removal of the offending glands can prevent the almost inevitable tragic outcome.

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## LOWER NEPHRON NEPHROSIS: CARBON TETRACHLORIDE POISONING WITH A REPORT OF 3 CASES

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LOWER nephron nephrosis is seen in association with renal damage following intravascular hemolysis due to sulfonamides, quinine and other antimalarials, arsine, abortifacient pastes, due to the action of the soaps on the blood and intravenous water<sup>6</sup>, incompatible transfusion, diabetic coma, concealed hemorrhage, prolonged labor, operations on the biliary tract, pneumonia, scarlet fever and diphtheria<sup>20</sup>, black water fever, transurethral prostatectomy, crush syndrome, non-traumatic muscular ischemia, electrical injury to muscle, heatstroke, uretero-placental damage, in alkalosis from excessive emesis, thermal burns and volatile poisons, especially carbon tetrachloride<sup>9,10,11,28,30,33</sup>, bleeding into the gastro-intestinal tract<sup>8</sup>, Porro cesarean<sup>18</sup>, possibly also with toluene<sup>7,11</sup> and rarely following mercurial diuretics<sup>4</sup>.

The classical description of the pathology of lower nephron nephrosis is given by Goodpastor<sup>17</sup>. One sees a large, pale, swollen kidney; on cross section the cortex is wide and pale. The disorder involves the distal portion of the nephron, the epithelium of the thick limb of Henle's loop and the distal convoluted tubules<sup>12</sup>. There are focal patches of cellular degeneration and necrosis<sup>12,17,24</sup>. Some lumina contain casts of a heme compound. Edema is present in the stroma of the kidney. Unfortunately for the patient in shock, the kidneys are part of the peripheral vascular system and, in an attempt to preserve the blood supply to the brain, the blood supply to them is decreased<sup>34</sup>.

In consequence, the duration of the shock or period of renal blood-flow shutdown is an important factor. It must be remembered that lower nephron nephrosis is a self-limited disease which, if survival occurs, will be followed ultimately by complete recovery of renal function and restoration of renal tubular histology. The mortality rate, however, is high; Lucké gives it as approximately 90%<sup>22</sup>.

When this condition is due to the inhalation of toxic fumes or the ingestion of poisonous substances there may also be damage to the liver<sup>28</sup>. Following the crush syndrome liver damage is also seen, with central necrosis<sup>30</sup>. In association with sulfonamides there may be extremely severe and persistent cerebral damage<sup>23</sup>. Luetscher and Blackman report 5 cases of lower nephron nephrosis following sulfonamide administration in which there were 3 deaths. Two patients who recovered showed only partial and very slow cerebral recovery.

With or without shock, depending on the etiological factor, the patient develops nausea, vomiting, weakness, malaise, sometimes pain in the abdomen or back, and either rapidly or insidiously, oliguria or anuria. Following this there is the development of edema (the degree of which will depend on the treatment), a rising blood pressure, rising non-protein nitrogen and acidosis, and death may intervene from either pulmonary edema or potassium intoxication<sup>19,27,29,32</sup>. During the course of the illness there may be

marked nervousness and tremulousness. During acidosis, tetany should not develop<sup>14,30</sup>, although total calcium does diminish. Calcium therapy must be carefully watched in this disorder<sup>26</sup>.

The reported figures for the blood urea nitrogen are startling and are roughly proportional to the duration of the oliguria or anuria. Barclay and Cooke<sup>5</sup> report a level of 340 mg. per 100 cc. in their case of barbitone poisoning followed by recovery. Dudley<sup>11</sup> reports a level of 302 mg. in a patient with carbon tetrachloride poisoning who had complete anuria for 10 days before recovery. Strauss<sup>30</sup> reports from the literature proven cases of renal shutdown wherein 1 patient lived 5 weeks, 2 lived 6 and 3 lived 7 weeks, and in 5 of these at autopsy there was no possibility of the formation of urine. The height of the non-protein nitrogen or the blood urea nitrogen will also depend to a certain degree on the therapy. If the patient is placed on a very restricted intake of fluids with a high carbohydrate or glucose intravenous medication, this will spare protein breakdown. It must be remembered that 37.5 gm. of protein leads to the formation of 6,000 mg. of non-protein nitrogen<sup>30</sup>, a mean daily rise of the non-protein nitrogen of 12 mg. per 100 cc. and of sulfate, phosphate and potassium of 1.86, 1.66 and 0.324 milliequivalents per day. Potassium rises more slowly because it is distributed throughout all the tissues. The anion concentration is consistently lower than the cation concentration for which at present no apparent reason exists. In addition to these chemical changes one must also remember that there is a definite hemorrhagic tendency as seen frequently in bloody fecal discharges, ecchymoses and purpura.

In the treatment of these patients it must be remembered that they will lose fluid only by evaporation and in the expired air, a total of about 1,000 cc.

daily. Because of gastric irritation, oral feeding is precluded and very shortly the slight carbohydrate reserves are exhausted. Then nutrition depends on protein and fat metabolism, approximately 70 and 200 gm. respectively daily, with resultant ketosis, azotemia and increasing potassium, sulfate and phosphate wastes. From the metabolism of these body stores there will be approximately 500 cc. of preformed water and water of oxidation. The average adult has roughly a 50 liter "pool" of fluid in his body in which to dilute these rising waste products. Gamble<sup>16</sup> points out the penalty of size in children when there is renal damage or loss of fluid. It is known that the larger the animal, the longer will be the survival period during anuria or oliguria; though the rate of formation of metabolic waste products is correlated with surface area (that is, a function of the total body metabolism), the fluid pool in which to dilute these products is a linear function of weight. It is dangerous to treat these patients with intravenous saline because this further increases the electrolytic concentration within the "closed" system and further increases the acidosis. Glucose aids metabolism of fats by curtailing ketosis.

The diversity of therapy for lower nephron nephrosis confirms the many faulty attempts to explain the pathological physiology and the many failures resulting in the high mortality rate. These include spinal anesthesia, splanchnic block, diathermy to the kidneys, Roentgen-ray to the kidneys, acetyl beta-methylcholine, irrigation of the kidney pelves, decapsulation, transfusion with compatible blood or plasma or both, intravenous sodium sulfate, hypertonic intravenous solutions, massive intravenous fluid therapy, peritoneal lavage, dialysis by the artificial kidney<sup>1,21</sup> and lavage of the intact gastrointestinal tract<sup>25</sup>.

It is quite apparent from the previous discussion that excessive fluid must be avoided in a one-way system, or pulmonary edema and death will result. The proponents of decapsulation claim excellent results but it must be remembered that they claim that anuria is due to the edema of the kidney and that with decapsulation there will be a release of this pressure and therefore an increase in the glomerular filtration. However, it must also be remembered that diuresis which occurs in recovery from this condition, occurs at the height of the edema. If edema were the cause of this condition, it should be remembered that no edema is present in the kidneys when the condition first begins. Talbott<sup>31</sup> decapsulated 1 kidney, inserted catheters in each ureter, and found that diuresis began on each side simultaneously.

Peritoneal lavage has had its advocates<sup>3,5,12</sup>. In the early stages of peritoneal lavage there is excellent removal of nitrogenous waste products. The experience of those who have used it indicates a decreasing dialysis of nitrogenous waste products proportional to the duration of the total lavage, peritonitis and mechanical difficulties with the apparatus. One must also consider the huge quantities of fluid passing through this system which may produce disastrous changes in the electrolytic and water balance. The initial enthusiasm for this procedure has markedly abated in recent years. Bassett *et al.*<sup>3</sup> found that though the non-protein nitrogen and serum inorganic phosphorus increased at first in the lavage, nevertheless, as the patient lost edema fluid, the values for these waste products in the blood rose above the pre-treatment level. They also noted the usual *post mortem* finding of peritonitis. One is reminded of Fishberg's classic statement, "treat the patient and not the blood chemistry"<sup>15</sup>.

Kolff<sup>21</sup> and Alwall<sup>1</sup> have developed

and brought the dialyzer to a great stage of efficiency. These machines are complicated and tricky, subject to considerable mechanical difficulties, require a trained team and still have many inherent difficulties in the maintenance of water and electrolyte balance. Kolff claims good chemical results but not too good clinical results.

Maluf<sup>25</sup>, through a modified triple-lumen Miller-Abbott tube, perfused the intestinal tract with a slightly hypertonic sodium sulfate solution, 30 cc. per minute. He claims that the results compare well with either lavage or dialysis, sulfate apparently replacing chloride to a large extent without observable injury.

Considering both the water of oxidation and the pre-formed water resulting from the metabolism of the patient's tissues and his daily loss, one limits the intake to 750 cc. of 10 or 15% intravenous glucose with sufficient heparin to prevent clotting of the needle and thrombosis, with excessive caution to prevent any infiltration of the hypertonic solution in the "already hypertonic" tissues. Salt is given to replace the chloride lost by emesis, equal quantities of saline being used to replace the salt vomited. In acidosis one may require sodium lactate. Where potassium determinations are impossible, indirect evidence may be secured from the electrocardiograph, but Tarail<sup>32</sup> warns that the electrocardiograph is not properly a substitute for the measurement of the concentration of serum potassium, although he finds some changes occur at potassium concentrations of 6.8 to 7.6 milliequivalents and there are consistent changes when the concentration of potassium is above 7.8 milliequivalents. Tall and peaked T-waves occur at 6 to 8 milliequivalents of potassium<sup>29</sup>, a depression of the S-T wave and a diphasic T-wave at 8 to 9 milliequivalents, and at these latter levels conduction is delayed and inter-

ventricular block occurs. Ventricular fibrillation, flutter or arrest occur at 14 to 16 milliequivalents<sup>27,29,32</sup>. Nadler<sup>27</sup> points out that U-waves appear in the electrocardiograph when the potassium blood concentration is below normal.

Burwell *et al.*<sup>6</sup> have emphasized that there are no recorded cases of death from lower nephron nephrosis if the patient lives 20 days. The disease is self-limited and the kidneys will begin to function of themselves. Then huge quantities of urine are excreted through the kidneys with associated loss of electrolytes, because the tubule, though intact, has not regained its acquired faculty of selective reabsorption. In consequence, during this recovery phase when the output is tremendous very frequent observations of the fluid output and of the blood chloride level must be made. Otherwise, extreme dehydration may result and what can be more serious, a marked hypochloremia. As a result of the hypochloremia convulsions can occur.

Because at this time the gastrointestinal tract has not yet recovered from its insult, the oral use of concentrated sodium or other chlorides is apt to produce considerable distress. This is a further reason for extreme care of the veins during the period of hypertonic glucose administration. Burwell<sup>6</sup> has advocated the use of normal saline to replace the salt in the urine and because of the prolonged venous therapy necessary in these patients has advised against the use of solutions more concentrated than 15%. In consequence the method of treatment will vary with the individual patient and his "venous status". In our Case 2 we used 5% saline to control the blood chloride level during the polyuric phase of recovery.

In reviewing the recent European literature on the so-called hepatorenal syndrome, one observes a marked similarity to lower nephron nephrosis.

Trier<sup>33</sup> reports a case of hepatorenal syndrome which might better be classified as lower nephron nephrosis due to carbon tetrachloride poisoning, in which, for a very short period, mild icterus was apparent. Barclay and Cooke<sup>2</sup> report a similar situation following the use of sodium barbitone.

**Case Reports.** CASE 1. Mr. E.B.I., age 22 years, was admitted to Kadlec Hospital April 1, 1948, for generalized aches and pain, nausea and vomiting.

The past history revealed the usual childhood diseases and influenza with hospitalization in 1947. The family stated that the boy began drinking heavily after discharge from the Navy in 1946 and that he was in the habit of going on periodic drinking sprees for several weeks at a time.

The present illness dates back to March 30, 1948, when 3 men cleaning offices used carbon tetrachloride to mop the floor. After 15 minutes of this the patient complained of headache and for the next 45 minutes walked in and out of the room. At the end of this time the 2 other men complained of headache and slight dizziness which disappeared soon after discontinuing the use of the chemical. When the patient started working at 4:00 p.m. on March 30, 1948, he complained to his companions that he had been sick on the preceding day and that he did not feel well on reporting to work that evening. On admission he was under the influence of alcohol and it was learned that he had had an extended alcoholic "binge" on the preceding evening.

Physical examination showed a moderately well developed white male complaining of vague muscular aches and pains but not critically ill. The nose and pharynx were slightly injected and there were tender and slightly enlarged submaxillary nodes in the neck. The eyes, ears, lungs, heart, extremities and reflexes were not remarkable. There was rigidity in the right side of the abdomen and an enlarged liver. Extremities and reflexes were normal, skin was dry. Temperature was 99.4° F., pulse 86, respirations 20, blood pressure 120/70.

The laboratory findings on admission showed hemoglobin of 14.5 gm., 4,700,000 red blood cells, 16,150 white blood cells (95% neutrophils and 5% lymphocytes); by the 5th of April, 12.5 gm. of hemoglobin, 3,890,000 red blood cells with slight anisocytosis. No urine was obtained until the 4th of April when it showed a specific gravity of 1.019, acid reaction, 2 plus albumin, 1 plus sugar, 1 to 2 white cells, few epithelial cells and

much amorphous material in the sediment. On the following day the urine showed a specific gravity of 1.012, alkaline reaction, 4 plus albumin, no sugar, 20 to 25 white cells, 0 to 2 red cells per high power field, 1 finely granular and 0 to 2 coarsely granular casts.

On the 2nd hospital day the blood pressure rose to 152/110. He was given rather copious amounts of intravenous fluid because of vomiting and anuria. On April 2nd he received 2,000 cc. of intravenous fluids, 2,500 cc. on the 3rd and 4,500 cc. on the 4th.

A surgical consultation was held on April 4th because of the persistent emesis, marked distention and rigidity of the entire right abdomen. At the suggestion of the surgeon, Wangensteen suction was instituted without any relief. The patient continued to vomit around the tube, even though the suction was draining well.

Early on the morning of April 5th he began to spit and vomit bloody mucus, became quite drowsy and edematous. During the day he continued spitting considerable bloody froth. Oxygen was administered by tent. At 6:00 p.m. the blood pressure was 170/0, the edema was increasing hourly. At 8:00 p.m. the blood pressure was 190/40. A venesection for relief of the pulmonary edema was unavailable. Petechiae were noted at this time in the conjunctivae. Slight temporary improvement in the respirations was obtained late that night by the use of 50 cc. of 50% glucose with 0.5 gm. aminophyllin intravenously. This procedure was repeated at 1:00 a.m. of April 6th. At 6:30 a.m. the blood pressure had risen to 170/80, and the pulse was full and strong. The edema of the face had completely disappeared but there were coarse bubbling rales throughout both bases. At 11:45 a.m. he had a slight convulsion, vomited a copious blood-stained fluid, became cyanotic and died at noon. During the entire hospital stay he had received 30,000 units of penicillin intramuscularly every 3 hours.

The urinary output was not measured until the 4th at which time he had 500 cc. of urine and 1150 cc. of emesis. On the 5th he had a urinary output of 260 cc. and 1900 cc. of vomited fluid.

At AUTOPSY, the liver weighed 2050 gm., was enlarged 6 cm. below the costal margin, displayed rounded edges, and on cross section showed typical passive congestion. The spleen weighed 270 gm., was enlarged to about twice normal size, but appeared otherwise normal. The left kidney weighed 290 gm. and the right 300, appeared slightly enlarged, on section the capsule stripped with ease and the surface looked moderately edematous. The left lung weighed 1150 gm. and the right

1400 gm., were deep red in color, barely floated in water and were markedly engorged with blood. On section the bronchi were filled with frothy blood-stained fluid and the lung tissue showed an advanced red hepatization.

The microscopic findings after autopsy showed a marked accentuation of the lobular markings and a distinct nutmeg appearance of the liver, which was firm, rubbery and hemorrhagic. The liver showed marked chronic passive congestion with fatty infiltration of the parenchyma. There was no evidence of a cirrhotic process. The renal glomeruli were unusually well preserved, the tubules showed a minimal degree of cloudy swelling. No casts, inflammatory exudate, nor other change was seen.

At the insistence of the consultant who saw him the evening before death, specimens of the liver, kidney and lung tissues were sent to R. J. Hale of the General Chemical Laboratory who reported that volatile organic chlorides were found in each specimen submitted; but no definite quantitative data were available. Specimens were also sent to Dr. E. T. Bell of the University of Minnesota who found severe central necrosis of the lobules of the liver and interstitial edema and hydropic degeneration of the tubules of the kidney, which findings he thought were consistent with carbon tetrachloride poisoning. Specimens sent to Dr. Tracy B. Mallory of the Massachusetts General Hospital were reported upon as follows: "The sections from the liver and kidney are entirely characteristic of carbon tetrachloride poisoning. The liver shows a sharp central necrosis without as yet evidence of regeneration. The kidney is a typical lower nephron nephrosis, with pigment casts, degeneration of the ascending limbs of Henle's loop, interstitial inflammation at the corticomedullary junction and foci of venous thrombosis. The synergistic effect of alcoholism in relation to carbon tetrachloride injury is well established, both experimentally and from clinical experience. It is very probable that it played a contributing role in this case."

CASE 2. C.R., a 36 year old well developed, well nourished white male was admitted to Kadlec Hospital on Dec. 25, 1948, in acute distress, complaining of aching in the upper abdomen, and nausea and vomiting of about 12 hours' duration. He had been a rather hard drinker since the age of 21 at which time he began to drink 2 to 3 quarts of whiskey weekly. On December 23, 1948, there was a fire in the insulation around the machinery of his icebox, for which he used a Pyrene fire extinguisher containing 25% carbon tetrachloride. This procedure occupied about 5 min-

utes, but because the space in which he was working was only about 2.5 by 2.5 by 0.5 feet, and he was down close enough to observe the fire, he received a very high concentration of carbon tetrachloride in these few minutes. He noted no ill effects that night but on the evening of December 24 he began to feel distressed, although he could not describe any definite symptoms. During the morning of Christmas day he had severe pain in the epigastrium and back which was associated with frequent and persistent vomiting, malaise and weakness. Around noon on Christmas day he began to note numbness of both arms. He also complained of distention. He was admitted to the hospital by ambulance.

His past history also reveals that he had been a dyer for many years. During the war he worked as an electrician and is still so employed, and though during the war he was in close association with welders he feels that he never was exposed to a very high nor prolonged concentration of toxic or metallic fumes. In spite of the copious amounts of emesis, he had not noted its character, although during the late part of the morning he was quite definite that it was only clear fluid. He has noticed for some time that on an insufficient

fluid intake, he may note some slight urinary burning, but otherwise has noticed no abnormalities in the genito-urinary system and as regards his slight urinary output during the past few hours, he felt that it was due to the copious and persistent vomiting. Four years ago when he allowed an insurance policy to lapse he was found to have a slightly elevated diastolic blood pressure.

The history of carbon tetrachloride poisoning, though persistently sought, was not elicited until about 5 days after admission when he thought of the fire and the fumes.

His height was 68½ in., weight 135 lb., temperature 99.4° F., pulse 105, respirations 20 and blood pressure 140/80. The local physical examination revealed a very tender epigastrium with definite rigidity and no rebound. Neither costovertebral angle was tender, although a fairly hard punch on the left side did cause some jarring disturbance. The remainder of the physical examination was not remarkable.

On admission the urine had a specific gravity of 1.007, acid reaction, 3 plus albumin, no sugar, 0 to 1 white blood cells, 0 to 1 red blood cells, many granular casts and much amorphous material. Hemoglobin was 14 gm.,

TABLE 1. URINE DATA, CASE 2.

| Date     | Intake<br>24 hr. | Output<br>24 hr.                     | Sp. Gr. | React.  | Albumin | W.B.C.<br>per hpf       | R.B.C.<br>per hpf | Miscellaneous                                      |
|----------|------------------|--------------------------------------|---------|---------|---------|-------------------------|-------------------|--|
| 12-25-48 |                  |                                      | 1.017   | acid    | +++     |                         |                   |  |
| 12-25-48 |                  |                                      |         | acid    | +++     | 1-3                     |                   | many granular casts                                |
| 12-26-48 |                  |                                      |         | acid    | +++     | 2-3                     |                   | many granular casts                                |
|          |                  |                                      |         |         |         |                         | 20-80<br>shadow   | 0-3 coarsely gran.<br>casts                        |
| 12-27-48 | 2300             | 10                                   | 1.016   | acid    | +++     | 0-2                     | 1-3               | 5-6 coarsely gran.<br>casts                        |
| 12-28-48 | 750+ic           | 53+20E                               |         | acid    | +++     | 6-8                     |                   |  |
| 12-29-48 | 750+ic           | 135                                  |         |         |         |                         |                   |  |
| 12-30-48 | 750+ic           | 135                                  |         |         |         |                         |                   |  |
| 12-31-48 | 750+ic           | 59                                   |         |         |         |                         |                   |  |
| 1-1-49   | 750+200t         | 45                                   | 1.005   | alk.    | +++     | 10-18<br>with<br>clumps |                   |  |
| 1-2-49   | 1000+480t        | 40                                   | 1.003   | alk.    | +++     | 8-12                    |                   |  |
| 1-3-49   | 750+ic           | 90                                   | 1.014   | alk.    | ++++    | 3-4                     | 7-10              |  |
| 1-4-49   | 1000+ic          | 125                                  | 1.009   | alk.    | ++++    | 2-4                     | 25-30             |  |
| 1-5-49   | 1000+280         | 180                                  | 1.006   | acid    | +++     | 20-30                   | 10-20             |  |
| 1-6-49   | 1000+LD          | 240                                  | 1.010   | acid    | ++++    | 5-7                     | occ.              | many finely gran.<br>casts filled with<br>bacteria |
| 1-7-49   | 1000+LD          | 550                                  | 1.009   | acid    | +++     | 6-8                     |                   |  |
| 1-8-49   | 1000+LD          | 1145                                 | 1.003   | acid    | ++      | 3-5                     |                   |  |
| 1-9-49   | 1530+LD          | 2615                                 | 1.018   | acid    | 0       |                         |                   |  |
| 1-10-49  | 500+LD           | 3330                                 | 1.008   | acid    | +       | 1-2                     |                   |  |
| 1-11-49  | 2215+RD          | 3425                                 | 1.011   | acid    | +       | 4-7                     |                   |  |
| 1-12-49  | 2315             | 3950                                 | 1.011   | acid    |         | 0-1                     |                   |  |
| 1-13-49  | 2080             | 3720                                 | 1.010   | acid    | +       | 0-1                     | 0-1               |  |
| 1-14-49  | 1850             | 5325                                 | 1.005   | acid    |         | 0-2                     | rare              |  |
| 1-15-49  | 2400             | 4030                                 | 1.006   | acid    | trace   | 2-4                     |                   |  |
| 1-16-49  | 2350             | 3800                                 | 1.002   | acid    | trace   | 0-1                     |                   |  |
| 1-17-49  |                  | 2050                                 | 1.008   | acid    |         | 0-2                     |                   |  |
|          |                  | (from mid-<br>night to<br>4:00 P.M.) |         |         |         |                         |                   |  |
|          | ic — icechips    |                                      |         | t — tea |         | LD — Liquid Diet        |                   |  |



with 4,500,000 red blood cells, 11,400 white blood cells (99% neutrophils, 1% lymphocyte). Roentgen-rays of the chest and flat film of the abdomen in an upright position were not remarkable. The probable diagnosis of penetrating ulcer was entertained and he was admitted to the surgical service.

Late that afternoon the urine was acid, 3 plus albumin, no sugar, 1 to 3 white blood cells, many epithelial cells, many granular casts and much amorphous material. There were 12,350 white blood cells (98% neutrophils and 2% lymphocytes). No record was kept of the urinary output during the remainder of Christmas day, but on the following day there was no urinary output. There was slight icterus of the sclerae. A specimen of urine examined on the 26th, but passed on the 25th, showed an acid reaction, 3 plus albumin, no sugar, 2 to 3 white blood cells, 20 to 30 shadow red blood cells, many epithelial cells and 0 to 3 coarse granular casts. On the 26th the white blood count had risen to 15,600 (96% neutrophils and 4% lymphocytes).

During the remaining portion of Christmas day he received 2,000 cc. of 5% glucose in saline intravenously. On the 26th he was allowed to have fluids freely by mouth. On the morning of the 27th the urine showed a specific gravity of 1.016, acid reaction, 3 plus albumin, 0 to 2 white blood cells, 1 to 3 red

blood cells, a rare finely hyalin cast and 5 to 6 coarsely granular casts. The white blood count was 10,725 (89% neutrophils, 7% lymphocytes and 4% monocytes). The icteric index on the morning of the 27th was 27.5 units, the carbon dioxide combining power 36 vol.%, the blood chlorides 400 mg. per 100 cc. and blood urea nitrogen 86.7 mg.

Inadvertently it was not realized that the urinary output had been zero and an intravenous pyelogram was done on the 27th which failed to show any excretion of the dye in 45 minutes. It was then realized that something had happened to the kidneys and intensive unsuccessful search was made in the history by numerous observers for definite history of chemical solvent or other toxic substance. Diagnosis of lower nephron nephrosis was entertained and he was transferred to the medical service.

On the 27th the vital capacity was 3.2 liters, or 74% of normal. There was evidence of fluid in the bases posteriorly. He was placed on a very conservative regimen, receiving 750 cc. of 15% glucose intravenously every 24 hours with sufficient heparin thereafter to prevent clotting of the needles. Vomitus was replaced quantitatively with saline intravenously and fluids by mouth were limited to ice chips at very infrequent intervals, only sufficient to keep the mouth from being uncomfortably dry. On the 28th the blood

TABLE 2. BLOOD DATA. CASE 2.

| Date     | Hgb. | R.B.C. | W.B.C. | P. | L. | M. |
|----------|------|--------|--------|----|----|----|
| 12-25-48 | 14   | 4.5    | 11,400 | 99 | 1  |    |
| 12-25-48 |      |        | 12,350 | 98 | 2  |    |
| 12-26-48 |      |        | 15,600 | 96 | 4  |    |
| 12-27-48 |      |        | 10,725 | 89 | 7  | 4  |
| 12-31-48 | 12.5 | 3.87   | 14,650 | 82 | 8  | 8  |
| 1-10-49  | 11   | 3.58   | 17,800 | 93 | 2  | 3  |

| Date     | CO <sub>2</sub><br>vol. % | Cl<br>mg. per<br>100 cc. | BUN<br>mg. per<br>100 cc. | A:G<br>gm. | Thymol<br>Turbid<br>Units | Ca<br>mg. per<br>100 cc. | Clot<br>Time<br>Min. |
|----------|---------------------------|--------------------------|---------------------------|------------|---------------------------|--------------------------|----------------------|
| 12-27-48 | 36                        | 440                      | 86.7                      |            |                           |                          |                      |
| 12-28-48 |                           | 430                      | 85.5                      | 3.98:1.46  | 7                         |                          |                      |
| 12-29-48 |                           | 440                      |                           |            |                           |                          |                      |
| 12-30-48 | 50                        | 440                      | 91.5                      | 3.7:1.5    | 5                         |                          |                      |
| 12-31-48 |                           | 450                      |                           |            |                           | 7.8                      |                      |
| 1-1-49   | 45                        | 450                      | 98.8                      |            |                           |                          |                      |
| 1-3-49   | 40                        | 380                      | 114.8                     |            |                           |                          | 4 1/4                |
| 1-4-49   |                           | 420                      |                           |            |                           |                          |                      |
| 1-5-49   | 36                        | 410                      | 152                       |            |                           |                          | 3 3/4                |
| 1-6-49   |                           | 340                      |                           |            |                           |                          |                      |
| 1-7-49   | 36                        | 360                      | 149.5                     |            |                           |                          | 4                    |
| 1-8-49   |                           | 320                      |                           |            |                           |                          |                      |
| 1-10-49  |                           | 620                      | 117                       | 3.65:1.95  |                           |                          |                      |
| 1-11-49  | 38                        | 580                      | 117                       |            |                           |                          | 8                    |
| 1-12-49  |                           | 570                      |                           |            |                           |                          |                      |
| 1-13-49  | 50                        | 560                      | 52                        |            |                           |                          | 12                   |
| 1-14-49  |                           | 570                      |                           |            |                           |                          |                      |
| 1-15-49  |                           | 570                      |                           |            |                           |                          |                      |
| 1-16-49  |                           | 550                      |                           |            |                           |                          |                      |
| 1-17-49  | 59.5                      | 550                      | 25.4                      | 6.31:2.57  | 7                         |                          | 3 1/4                |

urea nitrogen was 85.5 mg., blood chlorides 430 mg., thymol turbidity 7 units, albumin globulin ratio 3.98:1.46. Red cell fragility test was normal. There was no clinical evidence of icterus. The blood pressure was 190/80.

The fluid in the lungs did not change for several days. The blood chloride remained relatively constant at 440 mg., the urinary chlorides were being excreted at the rate of 3 to 4 gm. per liter.

On the morning of the 30th the blood urea nitrogen was 91.5 mg., carbon dioxide combining power 50 vol.%. During that afternoon the patient had a very severe tonic convulsive seizure during which he bit his lower lip severely and his convulsion did not respond to the usual intravenous sedatives. Intravenous calcium was given, immediately after which he went into a deep and untroubled sleep for about 30 minutes, following which he had no remembrance of the convulsion. The blood calcium at this time was 7.8 mg. and subsequently intravenous calcium therapy was started. The following day, because of some twitching of the face and a positive Chvostek sign, the intravenous calcium was increased to twice daily.

On the 31st the urine showed a specific gravity of 1.007, alkaline reaction, 4 plus albumin, 0 to 2 white blood cells, a few round epithelial cells. The hemoglobin had dropped to 12.5 gm., red blood cells to 3,870,000. There were 14,650 white blood cells (82% neutrophils, 8% lymphocytes, 8% monocytes, 1% eosinophils, 1% basophils). Blood chlorides were 450 mg. per 100 cc. Two doses of 100,000 units of penicillin were given intravenously, 12 hours apart for the infected necrotic patch on the lower lip. Humphrey and Jones<sup>20</sup> found that blood penicillin stays at a therapeutic level, after a single dose, for 5 days during a period of oliguria.

On January 1st the blood urea nitrogen was 98.8 mg. The patient was quite nervous and irritable. During this time and up through the 3rd of January the patient had been complaining of troublesome distention, but it was felt unwise to give him relief of the distention other than by low soap suds enemas as needed. On the 3rd he was passing mucus and blood from the rectum, and hemorrhoids which had been relatively asymptomatic, became painful. It was apparent that he was becoming more edematous and on January 5th the blood urea nitrogen was 152 mg. At this time the urine was beginning to form, as will be noted from the tabulations, and from this time his course may be said to follow his changing fluid and electrolyte balance.

On the 6th the chlorides had dropped to 340 mg. and it was decided to give him intravenous saline as well as oral sodium chloride in capsules. Oral sodium chloride made him quite distended and uncomfortable. At this time very slight infiltration of glucose had ruined the veins of the arms to the point of preventing further intravenous medication therein. At no time had the veins in the legs been satisfactory and a cut-down was not desirable. Except for troublesome distention in the days shortly after restarting oral food, about the 5th of January, and very painful arms, the recovery period was uneventful and he was discharged on January 17, 1949.

He was seen again on January 23, 1949, at which time he felt much improved but unfortunately had an upper respiratory infection. The blood pressure was 160/110, pulse 100, respirations 14. It was decided at the time to stop his excessive salt intake because his urinary output was approaching 1500 cc. per day. He was allowed to return to light duties. He was seen again on February 2, 1949, and the blood pressure was 146/94. His improvement had been steady and for 10 days he had been at a type of work in which he rated himself at 30% of his former efficiency. He was having no urinary difficulties whatsoever and his total output was about 1200 cc. per day. On February 25, 1949, he was complaining of headache and stiffness of all joints when starting motion, but "limbering up" shortly after motion was begun. Otherwise he had regained his former efficiency at full duties.

CASE 3. M.P., a 34 year old white American housewife, was admitted to Kadlec Hospital on February 3, 1949, with a complaint of nausea, vomiting diarrhea, generalized aches and pains and generalized weakness of 2 days' duration following a cold.

The past history revealed the usual childhood diseases, scarlet fever, rheumatic fever, "St. Vitus' Dance" and pneumonia in a mild form as a child. There have been 4 or 5 episodes of acute rheumatic fever since. She had a complete hysterectomy in June of 1948. There is an extensive alcoholic history.

On admission the physical examination revealed an acutely ill, depressed woman in a fair state of nutrition. Her temperature was 98.6° F., pulse 84, respirations 18 and blood pressure 110/50. The pupils were miotic, probably as a result of morphine. Otherwise the eyes, ears, nose, throat and chest were not remarkable. The abdomen revealed appendiceal and midline incisional scars. The muscles of the abdomen were tender throughout. The liver was irregular and was felt 3 to 4

cm. below the costal margin. The region of the gallbladder and, or, the liver was quite tender. Pelvic examination was deferred. The lymph nodes and breasts were negative. The muscles of the extremities ached on pressure.

On admission the blood count was 11.5 gm. of hemoglobin, 4,250,000 red blood cells and 20,100 white blood cells (89% neutrophils and 11% lymphocytes). There was slight anisocytosis of the red blood cells. The Kahn test was negative.

The temperature at 8:00 p.m. on February 3, 1949, was 102° F., pulse 100, respirations 24 and the blood pressure had fallen to 88/42. At 1:40 a.m. on February 4, it was noted that the patient was becoming rapidly worse; she was heard to gasp for a short while and expired 14 hours after admission to the hospital.

The internist's original impression was viral enteritis; he wrote "at the time of examination this morning her clinical condition in no way seemed critical." The sudden demise of this patient was extremely puzzling in the absence of the history of carbon tetrachloride poisoning and the internist entertained such diagnoses as uremia, pulmonary embolus, cerebral edema, purpuric manifestation in the brain secondary to some virus infection, meningitis, Waterhouse-Friederichsen syndrome.

After her death the husband related that about 4 days prior to admission the patient had used carbon tetrachloride to clean the furniture in her trailer.

At autopsy the body appeared jaundiced. The internal organs and serous fluids were jaundiced. The liver was smooth and very fatty, with marked fatty infiltration of the cut surface. Grossly, the kidneys were normal. The impression was hepatorenal syndrome in the absence of any abnormality of the adrenal glands.

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**Summary.** 1. The literature on carbon tetrachloride has been reviewed and 3 cases are reported. Two of the patients died within a short time of entrance to the hospital. One developed the full clinical picture of lower nephron nephrosis and recovered on conservative management.

2. The frequency of severe lower nephron nephrosis and, or, renal damage following carbon tetrachloride poisoning in the presence of chronic alcoholism is well exemplified by all 3 of these cases.

3. Ingestion of carbon tetrachloride attacks first the liver with apparent sparing of the kidney. Inhalation damages primarily the peripheral vascular system of which the kidney is a component.

4. The advantages and disadvantages of mechanical "chemical wash-out" therapy have been discussed.

5. The use of calcium therapy is stressed in this syndrome.

6. Conservative management must be stressed in a "*one-way-hypertonic-solution*" individual; in other words do not drown the patient whose kidneys are oliguric or anuric; the faulty chemistry cannot be corrected by flushing a one-way system without serious alterations in water and electrolyte balance.

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# A CLINICAL STUDY OF AN INSTITUTIONAL OUTBREAK OF ACUTE INFECTIOUS LYMPHOCYTOSIS

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ACUTE infectious lymphocytosis is a disease of unknown etiology, essentially benign in nature, and characterized by pronounced lymphocytosis and eosinophilia. It occurs both sporadically and in epidemic form.

Since the disease was first described by Smith in 1941<sup>12</sup>, there has been reported a total of approximately 93 cases, the largest series numbering 28 patients<sup>10</sup>. This includes 16 patients mistakenly reported by Reyeisbach and Lenert<sup>11</sup> as infectious mononucleosis. In 1944 Smith<sup>13</sup> suggested the possible contagious nature of the disease on the basis of a small family outbreak. Finucane and Phillips<sup>5</sup> pointed out the presence of the eosinophilia, in describing an institutional outbreak in a children's tuberculosis ward. The report by Duncan<sup>3</sup> of 2 cases in young adults indicated that the disease was not confined to the pediatric age group.

The occurrence of an epidemic of acute infectious lymphocytosis in a large institution caring for approximately 1400 mentally defective and epileptic patients of all ages, afforded an opportunity to study in detail over a relatively long period, a large number of affected individuals. The purpose of this paper is to report the results of various studies and the clinical course in 86 of the inmates who contracted the disease.

**SITE OF EPIDEMIC.** The Southbury

Training School, situated in rural Connecticut, was accommodating approximately 1600 inmates and employees at the time the outbreak was discovered. The inmates had a median age of 23 years (range 5 to 65 years), and were classified, on psychological, social and developmental criteria, as high (moron), middle (imbecile) and low (idiot) grade mental defectives, in the approximate proportion of 40%, 30%, 30%, respectively. They live in individual cottages of 25 to 80 capacity depending on the mental status and chronological age. Each cottage is a relatively self-contained unit, having its own kitchen, dining room and recreational facilities in addition to the sleeping quarters. Uncooked food and pasteurized milk are sent daily to each cottage from a common storehouse. The water for the entire institution is derived from two deep wells and is tested bacteriologically at regular intervals. There is considerable inter-group contact, especially among the high grade population, in athletics, school, movies and other social activities.

**DISCOVERY OF EPIDEMIC.** The first case was found in July, 1947, as a result of a routine blood count on J. C., a low grade epileptic boy who was receiving Tridione. The marked lymphocytosis and eosinophilia exhibited by this boy stimulated the study of three other children in adjoining beds

in the same dormitory, who also were found to have a somewhat similar blood picture. At about the same time, a suggestively similar blood count was found in a high grade boy living in a cottage situated in an entirely different section of the institution, a considerable distance from the low grade cottages. Although isolated, random blood counts taken in children throughout most of the cottages in the institution indicated a widespread distribution of cases, technical limitations made it necessary to confine our various studies to the following three groups: 1, A low grade cottage in which 43 inmates and one employee were affected; 2, A high grade cottage in which 32 inmates and one employee were affected; 3, A miscellaneous group of 11 high grade children from other cottages, and an additional employee.

**CLINICAL ASPECTS.** The benign nature of the disease was confirmed in this study. Few of the cases would have been discovered without the aid of frequent blood study surveys in the various cottages.

**Fever:** Nineteen children with the disease, on restricted activity in their cottages, had rectal temperatures taken twice daily for 6 weeks. Ten of these boys had temperature elevation of 101° F. or higher for variable periods. In 7 cases only one reading was elevated; in 3 cases, 2 or more temperature elevations, either consecutive or intermittent, were found. All of the children were examined at the time of the elevated temperatures without demonstrating other causes for the fever. It is of interest that in spite of temperatures of 102° or more, most of the affected children objected to having their activities limited. In previously published papers, fever has been reported in about 30% of the cases.

**Gastrointestinal Tract:** Gastrointesti-

nal symptoms occurred in about 5% of our cases, and were usually of a very mild nature, such as nausea, anorexia and mild abdominal pain. Vomiting occurred on only rare occasions. Abdominal pain may, however, be severe, and 2 patients have been reported by Smith<sup>13</sup> and Duncan<sup>4</sup> in whom the possibility of an acute abdominal condition was considered. A recent report<sup>10</sup> of an institutional outbreak described diarrhea as the most prominent symptom. This was not the case in our series. In fact, diarrhea was not observed in any of our patients.

**Respiratory Tract:** No specific respiratory tract symptoms were observed except for dry, non-productive coughs in 3 patients early in the disease which lasted for a few days. This was not associated with fever. In about 10% of the cases, marked pharyngitis with some discomfort was observed.

**Central Nervous System:** One patient was seen with symptoms suggestive of central nervous system involvement (Case 2, see below), including headache, stiff neck and vertigo. Similar cases have also been observed by others<sup>6,15</sup>. An increase in lymphocytes in the spinal fluid has been reported in isolated cases<sup>2,3,6,15</sup>, ranging from 20 to 90 per cmm. Only 2 spinal fluid examinations were carried out in our patients, both being within normal limits.

**Lymphatic System:** A slightly palpable spleen was found in only 2 patients. This was present for only a few days at the onset of the disease. In no case was there significant lymphadenopathy. Splenomegaly without lymphadenopathy has been previously reported in 5 patients<sup>1,9,14</sup>.

**Case Reports.** CASE 1. J. M., a 13 year old white, high grade boy was referred to the dispensary on August 13, 1947, by his cottage matron because of nausea, vertigo and malaise. The matron stated that for the past several days the boy "had not acted like his usual self". A white blood cell count estab-

lished the presence of the disease (Table 1).

TABLE 1. COURSE OF BLOOD PICTURE IN 2 REPRESENTATIVE PATIENTS

|          | Date  | White<br>Blood Count | %<br>Lympho-<br>cytes | %<br>Eosino-<br>phils |
|----------|-------|----------------------|-----------------------|-----------------------|
|          | 1947  |                      |                       |                       |
| J.M.     | 8-13  | 22,100               | 63                    | 13                    |
| (Case 1) | 8-17  | 32,500               | 69                    | 16                    |
|          | 8-19  | 43,900               | 61                    | 4                     |
|          | 8-21  | 25,300               | 66                    | 8                     |
|          | 8-26  | 35,100               | 53                    | 15                    |
|          | 8-30  | 22,000               | 43                    | 13                    |
|          | 9-4   | 19,800               | 50                    | 24                    |
|          | 9-9   | 40,800               | 38                    | 23                    |
|          | 9-16  | 7,700                | 28                    | 26                    |
|          | 9-23  | 12,300               | 38                    | 20                    |
|          | 10-7  | 9,200                | 43                    | 15                    |
|          | 11-8  | 14,100               | 42                    | 9                     |
|          | 1948  |                      |                       |                       |
|          | 1-20  |                      | 59                    | 4                     |
|          | 1947  |                      |                       |                       |
| R.M.*    | 8-23  | 10,350               | 69                    | 4                     |
|          | 8-26  | 20,300               | 75                    | 6                     |
|          | 8-30  | 76,800               | 69                    | 4                     |
|          | 9-1   | 62,400               | 68                    | 3                     |
|          | 9-4   | 63,600               | 89                    | 1                     |
|          | 9-9   | 67,800               | 86                    | 2                     |
|          | 9-16  | 77,400               | 83                    | 4                     |
|          | 9-23  | 66,800               | 83                    | 4                     |
|          | 10-7  | 13,600               | 45                    | 8                     |
|          | 10-27 | 10,900               | 39                    | 3                     |
|          | 11-18 | 16,800               | 44                    | 3                     |
|          | 1948  |                      |                       |                       |
|          | 1-5   | 11,400               | 57                    | 4                     |

\* A 12 year old boy with typical clinical course.

Upon admission to the institution's hospital for further study, the boy did not appear sick, although a slight non-productive cough was present. Physical examination was essentially negative, revealing only a thin serous discharge from the nares. There was no lymphadenopathy or splenomegaly. The boy's hospital course was relatively uneventful. However, he complained occasionally of vague abdominal pain to the right of the umbilicus where there was moderate tenderness, but no spasm or rigidity. In addition, for several days he vomited 1 to 3 times daily with no apparent preceding nausea. He was afebrile while in the hospital except for the 7th day when his temperature rose to 103 degrees, but returned to normal within 12 hours. The patient was discharged well on the 12th day.

Chest x-ray taken on Aug. 16, was indeterminate. Examinations for heterophil agglutinins on Aug. 17 and on Sept. 2 and

cold agglutinins on Aug. 21 were negative. Lumbar puncture on Aug. 19 was negative. Nose and throat cultures, nasal swabs for hemophilus pertussis, stool examination for ova and parasites, trichinella skin test, Mazzini serological examination, erythrocyte sedimentation rate, and several urinalyses were all non-contributory. Eosinophilia in this patient persisted for 3 months.

CASE 2. C. F., a 16 year old white, high grade male was admitted to the institution's hospital on Sept. 11, 1947, with fever and a stiff neck. He had felt "poorly" that morning and in the afternoon had become feverish, dizzy, and had a headache. He complained of difficulty in walking because of "stiff legs and back". On admission his temperature was 103.6°; physical examination revealed a markedly rigid neck with a positive bilateral Kernig's sign, physiological tendon reflexes and no evidence of muscular weakness. A lumbar puncture performed on admission was negative. The white blood count established the diagnosis of acute infectious lymphocytosis. The stiff neck was not apparent the day following admission and after an uneventful 7-day hospital course the patient was discharged entirely well.

CASE 3. J. N., a 12 year old high grade, white boy was admitted to the institution's hospital on Aug. 22, 1947, with fever and sore throat of 1 day's duration. On admission he was acutely ill with a temperature of 102°, and lethargic. Physical examination revealed only a moderately injected throat with enlarged tonsils. There was no lymphadenopathy. During his first 5 days in the hospital his temperature ranged between 100 and 103 degrees despite adequate sulfadiazine therapy. He felt perfectly well, however, and his only complaint was a feeling of soreness of the trachea just superior to the sternal notch. The spleen, although not felt on admission, became palpable on the 6th day, 4 cm. below the left costal margin and remained so for several days.

Chest x-ray on Aug. 26, was indeterminate. Examination for heterophil agglutinins on Sept. 1, and cold agglutinins on Sept. 9, were negative. Erythrocyte sedimentation rates taken while the patient was afebrile, and using Wintrobe's method were: 34 mm. on Aug. 27, 32 mm. on Aug. 29, and 12 mm. on Sept. 1.

LABORATORY FINDINGS. The outstanding features of the disease were the changes in the blood consisting of leukocytosis, lymphocytosis, and eosinophilia. These are graphically de-

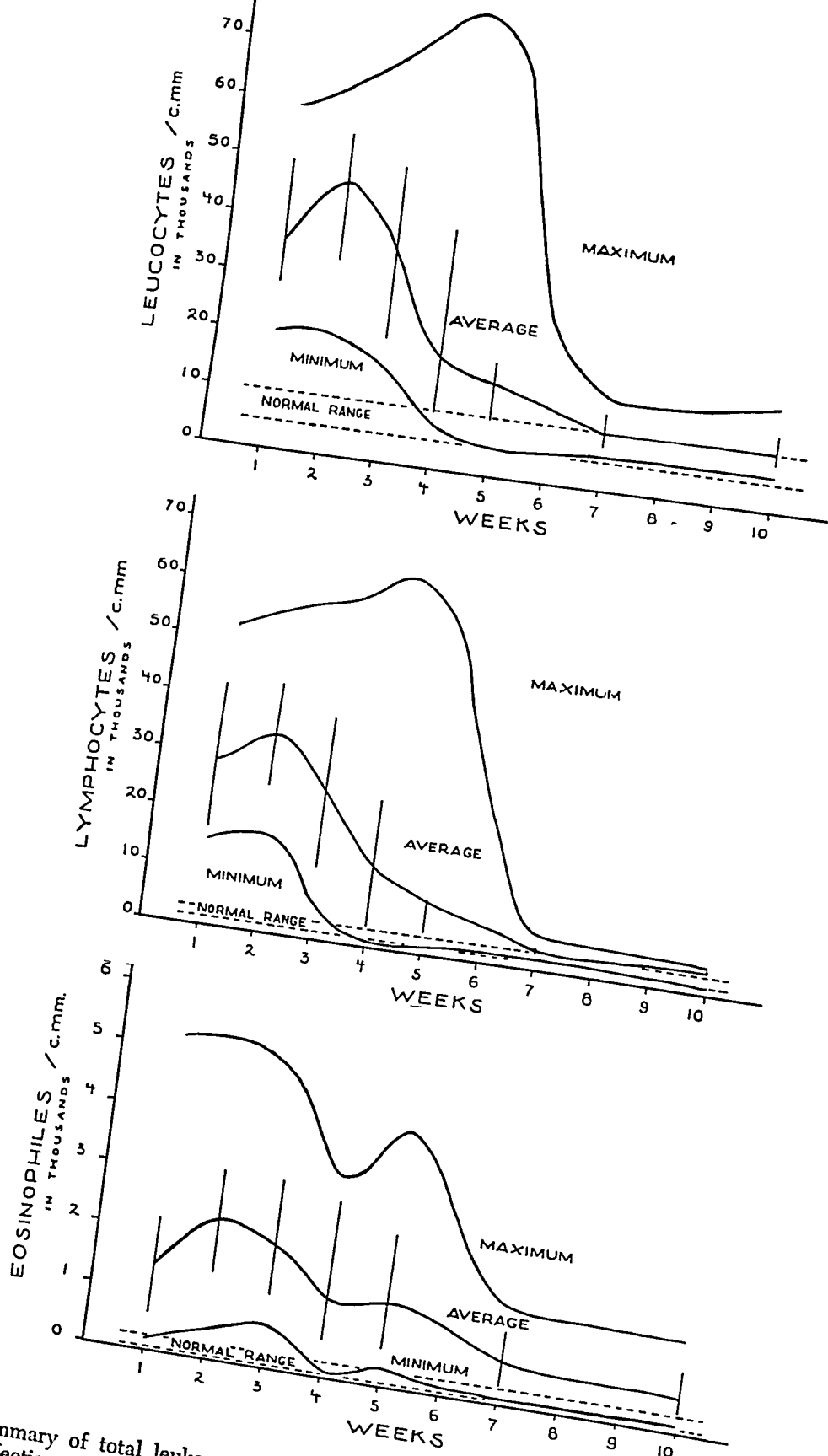


FIG. 1. Summary of total leukocyte, lymphocyte and eosinophil response during the course of Acute Infectious Lymphocytosis in 23 patients. The broken lines represent the accepted normal range. The average, maximum and minimum values are represented. The vertical lines indicate the range of values for the middle two-thirds of the 23 patients.



scribed in Figure 1, for 23 high grade patients. Table 1 gives the typical course of these blood changes in 2 individual cases.

*Leukocytosis.* A marked leukocytosis due to an increase in the number of lymphocytes was found in all the cases. The maximum white blood count in our patients was 77,400, with an average peak of approximately 47,000.

*Lymphocytosis.* The lymphocytosis was always striking, ranging between 60% and 93% at its height. For a valid interpretation of the differential count, it is essential to express the cellular components in absolute terms. The highest lymphocyte count was 64,000 per cmm., with an average peak of 34,000. The normal absolute value for lymphocytes is approximately 5,000 per cmm. The lymphocytosis persisted for an average period of 7 weeks. The lymphocytes were mainly of the small mature type showing a normal compact nucleus, although a great number exhibited a basophilic cytoplasm. Occasionally an atypical lymphocyte resembling a Downey Type I cell was seen.

The course of the leukocytosis and the lymphocytosis coincided almost identically (See Fig. 1). The leukocytic response differed in adults and children. The average white count peak for the 14 adults was 25,600 per cmm., contrasted with an average of 47,000 for the 23 children. This was true also of the lymphocytosis where the average highest absolute value for the adults was 16,000 and for the children 34,000.

*Eosinophilia.* An absolute eosinophilia was observed in all the cases and, in many instances, was extreme. The maximum absolute value was 5,300 eosinophils per cmm. with an average peak of 2,300, as compared to the normal absolute value of 400 or less. In isolated cases, not included in Fig. 1, an absolute eosinophilia as high as 7,-

800 per cmm. was encountered. The maximum eosinophilia, in relative values, was 32%. The average duration of eosinophilia was 10 weeks and, in a few cases, was still present after many months.

*Erythrocytes.* Red blood cells and hemoglobin at the height of the disease were found to be within normal quantitative limits in all our patients, and remained so during the course of the disease. Nucleated red blood cells, in the form of normoblasts, and varying from the basophilic to the orthochromic stages, were observed in many patients at the height of the leukocytosis, but only after diligent search.

*Platelets.* No significant changes in number and appearance of the platelets were noted on direct smears.

*Bone Marrow.* Sternal marrow examinations of 3 patients at the height of the illness are summarized in Table 3. The bone marrow exhibits a general hyperplasia. The lymphocytosis and eosinophilia present in the peripheral blood are seen to be a reflection of the increased production of these elements in the marrow.

*Lymph Nodes.* Although there was no lymphadenopathy in any of the patients, inguinal nodes were excised for histological examination from 2 patients (A. L. and L. B.) at the height of their disease. Since the microscopic findings were similar in both cases, the pathological description of one, A. L. a 13 year old male, follows: "The capsule and trabeculae are thin. Only occasional lymphocytes are present within the former and in the surrounding areolar tissue. The cortical sinusoids have their usual structure and there are broad interstices among the reticulum cells. The medullary sinusoids, however, show a marked degree of proliferation of stellate and spindle shaped reticulum cells. Among these are occasional lymphocytes and large erythrocytes. Within the cortex there

are large lymph follicles which are continuous with broad medullary cords. The lymphocytes are typical cells without an undue proportion of the larger elements. Scattered among them are large reticulum cells of the usual morphology and number. Germinal centers are large in some follicles and small in others. They exhibit no evidence of necrosis or of hyaline change.

*Diagnosis.* Lymph node showing moderate hyperplasia and proliferation of reticulum of medullary sinusoids. There are no pathognomonic changes by which acute infectious lymphocytosis could be recognized."

Smith<sup>14</sup> reported biopsies taken on

cervical and inguinal nodes of 2 patients with this disease. The outstanding features noted by him were proliferation of the lining reticulo-endothelial cells of the sinuses and varying degrees of hyaline degeneration of many of the germinal centers of the lymph follicles.

**ADDITIONAL LABORATORY DATA.** Mazzini serological tests were done on 38 patients and were all negative. Heterophil agglutination tests (Paul-Bunnell) performed on the same patients were also negative and remained so in several cases on repeated examinations.

Examination for cold agglutinins were done on 19 cases. Only 2

TABLE 2. SUMMARY OF LABORATORY FINDINGS

|                       | Present Series      | Previously Reported Cases       |
|-----------------------|---------------------|---------------------------------|
| Leucocytosis          |                     |                                 |
| Maximum number        | 77,400 per cmm.     | 147,000 per cmm.                |
| Average Duration      | 49 days             | 30 days                         |
| Lymphocytosis         |                     |                                 |
| Maximum %             | 93                  | 97                              |
| Average Duration      | 49 days             | 30 days                         |
| Eosinophilia          |                     |                                 |
| Absolute              | All cases           | All cases                       |
| Average Duration      | 10 weeks            | Not reported                    |
| Maximum Duration      | Over 5 months       | 7 months                        |
| R.B.C. and Hemoglobin | Normoblasts noted   | No abnormalities                |
| Platelets             | No changes noted    | No changes noted                |
| Bone Marrow           | Increased (3)*      | Normal to slight increase       |
| Total Count           | Increased (3)       | Normal to increased             |
| % Lymphocytes         | Normal to increased | Normal to increased             |
| % Eosinophils         | Negative (38)       | Negative                        |
| Heterophile Test      | Negative (38)       | Negative                        |
| Serology              | Negative (19),      | Negative                        |
| Cold Agglutinins      | Suspicious (2)      |                                 |
| Erythrocyte Sed. Rate | Normal (8)          | Normal                          |
|                       | Increased (7)       |                                 |
| Cerebrospinal Fluid   | Negative (2)        | Pleocytosis (5)<br>Negative (1) |

\* Figures in parenthesis refer to the number of examinations performed.

TABLE 3. RESULTS OF STERNAL BONE MARROW EXAMINATIONS IN 3 PATIENTS

|                                | Normal *<br>Average % | Case<br>C. C. | Case<br>A. I. | Case<br>A. J. |
|--------------------------------|-----------------------|---------------|---------------|---------------|
| Lymphocytic series             | 10.0                  | 15.5          | 28.5          | 17.0          |
| Eosinophilic series            | 3.5                   | 10.5          | 4.5           | 11.0          |
| Other nucleated W.B.C.         | 64.5                  | 49.5          | 44.5          | 54.0          |
| Nucleated R.B.C.               | 22.0                  | 24.5          | 22.5          | 18.0          |
| Total Nucleated cells per cmm. | 150,000(?)            | 452,000       | 437,000       | —             |

\* From Wintrobe, M.N., Clinical Hematology, Philadelphia, Lea & Febiger, 1942.

showed elevated titers of 1:64 and 1:32; the latter was found to be 1:16 a week later. Erythrocyte sedimentation rates, using the Wintrobe method and correcting to hematocrits of 42%, were performed on 15 afebrile boys under 13 years of age. Seven had rates above 10 millimeters, but only one was greater than 20 mm. (Case 3).

Stool examinations for ova and parasites on 12 patients were negative, except for 2 whose stools contained ova of *Oxyuris vermicularis*. The latter are occasionally found in routine institutional stool examinations.

Skin tests for *Trichinella spiralis* on the 15 cases exhibiting the most pronounced eosinophilia showed only one with a positive reaction. Urinalyses on 17 patients were negative.

Chest films taken on 6 patients at the height of the disease were indeterminate.

Table 2 summarizes all of the above pertinent data.

**TREATMENT AND PROGNOSIS.** There was no evidence that the clinical course of the disease was in any way affected by sulfadiazine or penicillin. The treatment was entirely symptomatic. All patients made an uneventful recovery and there were no complications.

**EPIDEMIOLOGY.** *Age and Infectivity:* The age range of the 87 patients included in this study was from 5 to 56 years. Fourteen of these patients were 17 or more years of age. There were no children under 5 years in the cottages studied.

In the 2 cottages that were studied in detail, there were 134 patients and

employees. Of this number 76 (57%) contracted the disease. The relationship of age to the incidence of the disease is given in Table 4. There was no significant difference in the incidence of infection in the 3 age groups. It is apparent that the disease seen in this outbreak was exceedingly contagious.

*Sex and Color.* An analysis of sex and color is limited since the group studied consisted mainly of white males. However, there were 2 females and 3 negroes affected, and these were in approximate proportion to the number exposed.

*Incubation Period.* Adequate information relative to the incubation period was difficult to obtain. The date of exposure of individual cases was impossible to determine because of the intermingling of the children in the cottages and throughout the institution. In addition, the onset of the disease could only be established by daily blood examinations on large numbers for relatively long periods, a technical procedure which was not feasible in the present study. However, the date of exposure and the approximate onset of the disease were determined in an 11 year old boy from an outside community who developed the disease 16 days after known exposure. Smith<sup>14</sup>, estimated the incubation period to be between 12 and 21 days.

*Etiology.* Nose, throat, and stool cultures revealed no significant pathogenic microorganisms. Innoculation of chick embryos and of mice intraperitoneally with blood serum from 6 patients at the peak of the disease revealed no recognizable virus.

**DIFFERENTIAL DIAGNOSIS.** From a practical viewpoint, the importance of this disease stems from its possible confusion with other conditions carrying more or less serious prognostic implications. A detailed and complete discussion of the differential diagnosis

TABLE 4. ANALYSIS OF INFECTIVITY AT VARIOUS AGE LEVELS IN 134 INHABITANTS OF 2 COTTAGES

| Age         | Number Exposed | Number Affected | Percent Affected |
|-------------|----------------|-----------------|------------------|
| 5-10 years  | 51             | 30              | 59%              |
| 11-16 years | 65             | 35              | 54%              |
| 17-56 years | 18             | 11              | 61%              |

has already been presented elsewhere<sup>12,9,14</sup>. This will be reviewed briefly.

*Lymphatic Leukemia.* This has been the initial tentative diagnosis in a number of the reported cases of acute infectious lymphocytosis<sup>4,7,12</sup>. However, the benign clinical course, the absence of hepatomegaly, significant splenomegaly, lymphadenopathy, anemia and thrombocytopenia, as well as the normal appearance of the lymphocytes are sufficient in all cases to distinguish the 2 conditions.

*Infectious Mononucleosis.* This is readily differentiated by the absence of enlargement of the lymph glands spleen and liver, as well as the relative rarity of atypical lymphocytes. The combination of marked lymphocytosis and eosinophilia are not seen in infectious mononucleosis. The presence of a positive heterophil agglutinin reaction helps confirm the latter diagnosis.

*Miscellaneous Conditions.* Other causes of lymphocytosis or eosinophilia such as pertussis, trichinosis, chronic infections like tuberculosis and brucellosis, convalescence from certain acute infections, and so on, should not present any significant difficulty. This is also true for the allergic conditions, other parasitic infections, and certain of the skin diseases.

*Discussion.* The epidemic described above demonstrated very well 3 characteristic features of the disease, namely, 1, the marked infectivity, 2, the paucity of significant symptomatology and physical signs, and 3, the relative uniformity of the hematological picture.

While we were able to identify 87 cases, there is little doubt that a considerably larger number would have been found if the entire population could have been studied. In the 2 cottages that were most closely followed, well over 50% of the exposed individuals contracted the disease. It is interesting that a clinical condition with this

degree of infectivity, and with so striking a blood picture, was not generally recognized and described prior to 1941. Recent publications<sup>8</sup> and personal communications from physicians both in this country and abroad would indicate that the disease is by no means rare, and is widely distributed throughout the world.

The observation of a relatively uniform incidence among the various age groups (Table 4) is of considerable interest. In general, our inmate and employee population, drawn from the relatively small area of western Connecticut and representing an indigenous population may not have been previously exposed to this disease. On the other hand, it is also possible that the condition does not confer a lasting immunity. Because of our opportunity to follow these individuals for relatively long periods, the answer should eventually present itself.

The blood findings in all cases were consistent and characteristic. Although the name of the disease stresses the lymphocyte reaction, the absolute increase in eosinophils is equally striking. Perhaps the tendency to describe the various leukocytes in the blood in relative terms has tended to obscure the presence of the marked eosinophilia which is invariably present at some time during the course of the disease. An interesting observation is the relatively long periods during which these blood findings persist, in many cases for as long as 4 months, and occasionally longer.

The failure of the neutrophils to exhibit any significant absolute quantitative change in the face of the markedly stimulating effect of the noxious agent on the lymphocytes and eosinophils is not due to any specific inhibitory effect on these cells. This is demonstrated by the course of the blood picture in a 20 year old boy who developed a typical pneumococcus

lobar pneumonia during the course of his infectious lymphocytosis. A rapid and striking absolute increase in the polymorphonuclear cells occurred and persisted until the usual penicillin response was obtained.

The appearance of nucleated red blood cells during the course of acute infectious lymphocytosis, although in very small numbers, was quite consistent. This has not been previously reported. Although its significance is not clear, it may represent a "crowd-

ing out" effect of these immature cells by the hyperplastic bone marrow.

Summary. The findings, both clinical and laboratory, in an institutional outbreak of acute infectious lymphocytosis, during which 87 cases were definitely identified, are summarized. Hematologically, the absolute increase of both lymphocytes and eosinophils was found to be pathognomonic and to persist for relatively long periods. The benign clinical course was confirmed. The markedly contagious nature of the disease was strikingly demonstrated.

The authors wish to express their indebtedness to Drs. David H. Clement, Averill A. Liebow and John R. Paul, of the Yale Medical School, for their assistance in this study.

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# CLINICAL EXPERIENCES IN PARKINSONISM WITH A NEW TYPE OF ANTISPASMODIC, 3-(1-PIPERIDYL)-1-PHENYL-1-CYCLOHEXYL-1-PROPANOL HYDROCHLORIDE ("ARTANE")\*

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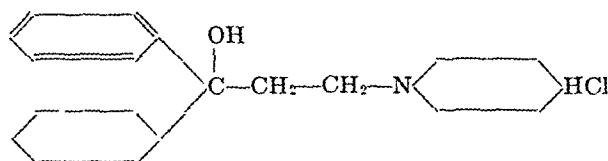
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IN recent years varying degrees of success have been reported following the administration of several new drugs to patients with parkinsonism. However, psychological factors in these subjects are such that many of them respond favorably for a time to almost any medication, thus making it difficult to appraise clinically the action of a particular agent.

In the present series of cases, a

and half that of atropine. It is mildly excitant to the central nervous system but much less so than atropine. Salivation is but slightly inhibited. There are no histamine-like qualities; on the contrary a feeble anti-histamine activity has been demonstrated. For these reasons it was believed that Artane in therapeutic doses might have fewer "side reactions" than effective doses of belladonna and its derivatives.



new drug, 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride, commonly called Artane\*, with graphic formula as noted below has been tested for its influence upon parkinsonism.

Artane is a member of a new series of antispasmodic compounds<sup>1</sup>. Its use in the treatment of parkinsonism was suggested by an analysis of its pharmacological properties in animals<sup>2</sup>. On isolated intestinal loops, its relaxant action is 20 times as great as trasentin

**Methods and Materials.** Twenty-three patients with parkinsonism were treated with Artane for periods varying from 10 to 46 weeks (Table 1). Of these 17, 15 men and 2 women, belonged in the postencephalitic, and 6, 2 men and 4 women, in the idiopathic or arteriosclerotic group. Of the former, 7 recall an attack of the "flu" toward the end of World War I and 10 remember having had sleeping sickness. The ages of the patients at the time of treatment with Artane ranged from 30 to 78 years with an average age of 56 years.

Seven of the postencephalitic group of subjects were being treated with atropine and

\* This drug was supplied to us by Dr. Guy Clark, Lederle Laboratory, Pearl River, N. Y., whose courtesy is herewith gratefully acknowledged. Use of the trademark name Artane in this article seems desirable as there is at present no other substitute for the lengthy chemical name. As the name was originally used to describe a group of drugs, this drug was earlier designated Artane 275C.

5 with hyoscine immediately prior to treatment with Artane. Two of the arteriosclerotic group were receiving hyoscine. These drugs afforded a mild to fair degree of control for the varied symptoms from which patients of both groups suffered. The remainder of the patients had been given similar medication at one time or another with little improvement. However, in no instance had any of them received a drug for the parkinsonism during the month immediately preceding treatment with Artane. Eleven of the 12 patients who were under treatment with atropine or with atropine and hyoscine were

deprived of all medication for 3 days prior to starting the Artane therapy. These 11 patients lapsed into an exaggeration of their symptoms at the end of this 3 day period.

All but 2 of the patients were then started on 2 mg. of Artane 3 times daily; these were given 2.5 mg. 4 times daily and 5 mg. 3 times daily, respectively.

**COURSE AND RESULTS OF THERAPY.** Within the first 3 days of therapy, 21 of the 23 subjects were much improved, and those previously taking atropine

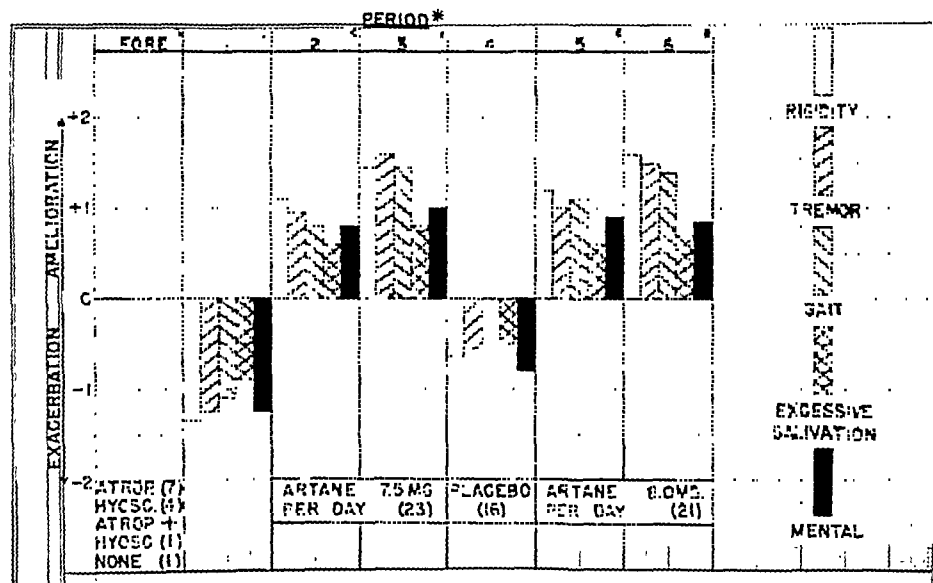


FIG. 1. Clinical Experiences in Parkinsonism with a New Type of Antispasmodic, 3-(1-Piperidyl)-1-Phenyl-1-Cyclohexyl-1-Propanol Hydrochloride ("Artane-275").

\* The numerals at the top of each column refer to specific periods of time:

FORE—A widely varying control period.

1. Three day period without medication.
2. First week of Artane.
3. Maximum effect of Artane.
4. Placebo, third day.
5. First week after return to Artane.
6. Maximal effect after return to Artane.

The base line of zero (0) indicates the status of the patient for each individual rubric before receiving Artane, i.e., the condition as observed when under no treatment or when receiving hyoscine or atropine. A minus one (−1) indicates mild to moderate exaggeration of the symptom, while a minus two (−2) indicates marked exaggeration. Similarly, plus one (+1) indicates a moderate degree of improvement and plus two (+2) a marked improvement.

a. Numerals in parentheses indicate the number of cases.

b. Data in period 1 represent only those patients who had been receiving treatment of some type during the "fore" period.

c. Periods 2 and 5 represent effects of Artane during first week of use. Periods 3 and 6 represent maximum obtainable effects, usually seen by end of 2d week.

or hyoscine felt as well if not better than they had while using maximum tolerated doses of these drugs. By the end of 1 week all were in better condition in most respects than they had been with previous medications. At the end of the second week there was further improvement. Then there was a "leveling off" with little increase in effects by raising the daily dose from 6 to 8 mg. However, improvement was maintained indefinitely without the development of tolerance or a "wearing off" effect. At least this statement

month period of treatment with Artane. The third patient with such crises was improved, as her attacks appeared about 1/5 as frequently as before treatment was instituted.

Improvement in the emotional status of the patient was observed in 19 instances. There was an increased "sense of well-being." The subject seemed more cheerful, more alert and more interested in his surroundings. Three persons showed no emotional or mental improvement, and one, whose manifestations will be discussed later,

TABLE 1. SUMMARY OF EFFECTS OF TREATMENT OF PARKINSONISM WITH ARTANE

| Manifestation        | Total Cases | Improvement |        | No Improvement | Remarks   |
|----------------------|-------------|-------------|--------|----------------|---|
|                      |             | Marked      | Slight |                |   |
| Rigidity             | 23          | 12          | 10     | 1              |   |
| Tremor               | 23          | 15          | 5      | 3              |   |
| Gait                 | 23          | 11          | 6      | 6              |   |
| Excessive Salivation | 18          | 7           | 4      | 7              | 5 cases never had excessive Salivation  |
| Oculogyric Crisis    | 3           | 2           | 1      | 0              | Of 3 cases who had had oculogyric crises, 2 never had any during 10 months with Artane and both frequency and duration were markedly reduced in the other case. |
| Mental Attitude      | 23          | 10          | 9      | 4              | 1 patient became nervous and another who was senile and disoriented became more confused with moderate (6 to 7.5 mg.) doses of Artane.                          |

holds for the period of 10 months that most of our subjects have been under continuous observation. They are summarized in Table 1 and Fig. 1.

There was a marked diminution of muscular rigidity in all patients, a decreased intensity of tremor in 20 and an improvement in gait in 17. Of the 18 subjects who initially suffered from excessive salivation and drooling, 11 were partially or completely relieved thereof and 7 saw no improvement in these manifestations. In 2 of 3 subjects, oculogyric crises disappeared entirely during the 10

became much confused while taking the Artane.

After 10 weeks of treatment with Artane, 9 patients were given a placebo. In physical characteristics, this placebo resembled the Artane and was similarly packaged with a distinguishing lot number so that nurses and attendants were unaware of its true nature. Within 3 days most of the patients showed the effects of the withdrawal of Artane (Fig. 1). Many of the patients who had been walking about the ward while receiving Artane were again confined to bed. They



stated that their muscles had "tightened up" and that they felt weak. Some said they had difficulty in swallowing. One developed an aspiration pneumonia which was successfully treated with penicillin. Some had a noticeably increased difficulty with articulation. The majority became apprehensive and wanted to know what was happening to them, as "the drug" seemed no longer "to be working." The tremors increased and salivation, even to the point of drooling, recurred. The majority again experienced greater difficulty in feeding themselves and in drinking without spilling. Those that were still walking were more handicapped in this regard than while under treatment.

These patients had regressed so dramatically by the end of 3 days that they were returned immediately to therapy with Artane. Three days later they had recovered a major portion of their lost ground. By the end of 1 week after returning to the use of Artane, they had almost regained the progress previously made by the aid of that drug. Before the end of the second week they had again achieved the maximum of improvement previously obtained. They no longer showed a look of apprehension but instead seemed fairly cheerful. Drooling stopped or diminished; rigidity and tremors were lessened; gait was improved and they were better able to feed themselves.

At a later date, in 7 additional patients, placebo was substituted for Artane without their knowledge. Their experiences were similar in all particulars to those of the first group of 9 subjects so treated. They went "down-hill" in 3 days and were returned to treatment with Artane at the end of that time.

In 15 patients, periodic determinations were made for blood sugar, creatinine, and urea nitrogen. Routine

urinalyses and complete blood counts were simultaneously performed. These examinations were carried out at first weekly, later semi-monthly and finally monthly. In no instances were there significant changes in the results of any of these tests.

**TOXIC REACTIONS TO ARTANE.** One man and 1 woman, ages 76 and 54 years, respectively, showed some unfavorable reactions due to Artane. The man belonged in the arteriosclerotic group and had been disoriented with memory defects prior to the medication. During the second week, when he received Artane at the rate of 9 mg. per day, his disorientation and confusion were further aggravated. Fecal incontinence developed and he fell several times while walking. In spite of these disturbances, there was some improvement in other respects. His rigidity and tremors decreased; he moved and walked faster. One week after discontinuing Artane he was in *statu ante quo*. At a later date following the use of 7½ mg. of Artane per day the same unfavorable reactions recurred. Again he was deprived of Artane and again returned promptly to his former condition. A few weeks later he was tried with a single dose of 2½ mg. per day. Mild improvement occurred in symptoms such as rigidity, tremors and gait; no unfavorable reactions appeared.

The 54 year old woman who developed a reaction to Artane belonged in the post-encephalitic group of subjects, and was not able to take 1.25 mg. of the drug daily without developing nausea, dizziness and, or, vomiting. The drug was tried in 3 different guises on 3 different occasions, always with the same result. That this was a central rather than a local gastric effect was demonstrated by the fact that administration of the drug in an enteric coated capsule did not prevent the appearance of symptoms.

In order to test human tolerance for the drug, 5 cases were selected to receive gradually increasing doses. The daily amount was raised from the initial level of 8 mg. to 15, 18, 20, 22, 24, 26, 28 and 30 mg. respectively at weekly intervals. When 18 mg. were given daily, one 30 year old woman developed blurring of vision. The same symptom occurred in a second subject, a man 37 years old, when 20 mg. were ingested daily, and in a third patient, a man of 60 years, when 28 mg. were taken daily. Upon the exhibition of these symptoms, these 3 patients were returned to their former dose of 8 mg. daily, with complete relief of symptoms. With this reduction of dosage, there was a transient increase in salivation, which returned to its former basal level of improvement after 3 or 4 days without any further alteration in treatment. The 2 remaining cases have shown no symptoms of a toxic nature despite the fact that they have now been on very large doses of the drug for 8 weeks and on 30 mg. daily for 1 week. One observation has puzzled us. In doses of 20 mg. daily and more, the Parkinsonian phenomena were not quite so well controlled as when lower doses were used. This statement applies particularly to the rigidity, tremors and gait. What significance has this phasic action?

**Summary.** Twenty-three patients, 17 with postencephalitic and 6 with arteriosclerotic parkinsonism were treated with Artane. All cases showed some improvement and most of them a marked improvement over and above their status under either atropine or hyoscine therapy or a combination of the two. The greatest changes were observed in the rigidity, tremors,

drooling, gait and mental outlook. Of the 3 cases that had had oculogyric crises, 2 were free of attacks for the 10 months during which Artane was administered. In the third subject they were lessened in frequency and shorter in duration. Two subjects developed unfavorable reactions, which disappeared promptly following cessation of therapy. No changes of pathological import were observed under Artane therapy in the blood counts, urinalyses, or blood chemical constituents (sugar, urea nitrogen, and creatinine) of any of the subjects.

**Conclusions.** It is held that Artane is a valuable medicament for the amelioration of symptoms of parkinsonism, probably more so in the postencephalitic subject than in the arteriosclerotic patient. Its chief advantage over the antispasmodics in common use, particularly those of the belladonna group, lies in the wider margin existing between the effective and toxic doses. For instance, Artane in therapeutic doses does not cause annoying dryness of the throat or blurring of vision; belladonna frequently does.

Another advantage of Artane over the belladonna preparations is the absence of any tolerance to its salutary effects. The doses do not have to be continuously increased in order to maintain its action.

The effective safe daily dose of Artane was found to lie between 6 and 15 mg. Toxic symptoms, such as blurring of vision, were first in evidence when 18 to 20 mg. per day were employed.

In general one may say that Artane has made life more endurable for these patients than it had been with previous types of medication.

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# THE ASSOCIATION OF HYPOPROTEINEMIA WITH SEVERE TROPICAL SPRUE\*

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For generations, tropical sprue has been regarded as a chronic wasting disease which occurs in tropical countries and is characterized by glossitis, diarrhea, and steatorrhea<sup>1,3,4,5,6</sup>. Persons with tropical sprue may have no anemia, or they may have a macrocytic or a microcytic anemia. The pathogenesis of the syndrome is not clearly understood and for that reason many theories have been advanced to explain its causation. Most of the theories have attempted to explain the disease as an infection or as a nutritional deficiency. For the past 3 years the authors have been studying tropical sprue in Cuba in an attempt to throw some light on its etiology<sup>7,8</sup>. This general study is being continued but because there have been so many patients who have given a

history of a low protein intake and because so many have had edema, a special study of the plasma proteins has been made. It is this aspect of the study of tropical sprue which is being reported at this time.

**Materials and Methods.** The authors arbitrarily selected 155 cases of tropical sprue for study, using the following 8 criteria: 1, Macrocytic anemia; 2, Red blood count of 2.5 million or less; 3, Color index of 1.0 or more; 4, Megaloblastic arrest of the sternal bone marrow; 5, Flat oral glucose tolerance curve; 6, Free hydrochloric acid in the gastric contents after histamine stimulation; 7, "Fatty stools"; 8, Weight loss.

From these 155 patients with tropical sprue, 121 were selected for study of their plasma proteins. Their red blood cell and hemoglobin levels were especially low and they had either clinical evidence of edema or a dietary history suggesting a low protein intake. Plasma protein studies were made by the method of Greenberg<sup>2</sup>.

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Eighty of these patients had total plasma protein levels of 6.0 gm. per 100 cc. or below and 41 had levels above 6.0 gm. per 100 cc. (The 41 patients with levels above 6.0 gm. were excluded from further study of their protein metabolism but were studied intensively as to their blood regeneration.) The 80 patients with total protein levels of 6.0 gm. or below were selected arbitrarily for further study of their protein metabolism. Of these patients, 22 were females and 58 were males. One of the females was under 20 years of age; 2 were between 21 to 30 years; 3 between 31 to 40; 4 between 41 to 50; 6 between 51 to 60; 6 between 61 to 70. Seven of the males ranged in age from 30 to 40 years; 9 from 41 to 50; 11 from 51 to 60; 24 from 61 to 70; 7 from 71 to 80.

The patients were hospitalized in a special ward for sprue and were under constant supervision and observation. From the day of their admission throughout the course of the study they were restricted to a diet consisting only of bread, cereals, viandas (root vegetables grown in Cuba), fruit, sugar, and coffee.

When the baseline determinations of red blood cells, white blood cells, hemoglobin, reticulocytes, and plasma proteins were completed, the patients were given folic acid. All except 1 patient were given from 10 to 100 mg. by mouth daily for from 10 to 160 days. One patient received 1 injection of 50 mg. of folic acid and 34 days later a second injection of 15 mg.

**Observations.** With an average of 2 or more plasma protein determinations in each case, the total protein was 6.0 gm. per 100 cc. or under in each case. In no case was the total protein below 3.0 or over 6.0 gm. Five cases had total protein between 3.0 and 3.5 gm.; 11 between 3.6 and 4.0 gm.; 15 between 4.1 and 4.5 gm.; 12 between 4.6 and 5.0 gm.; 11 between 5.1 and 5.5 gm.; and 26 between 5.6 and 6.0 gm. In 14 cases the albumin ranged from 1.5 to 2.0 gm.; in 31 cases from 2.1 to 3.0 gm.; in 29 cases from 3.1 to 4.0 gm. and in 6 cases from 4.1 to 5.0 gm. The globulin in 22 cases ranged from 0.5 to 1.5 gm.; in 24 cases from 1.6 to 2.0 gm.; in 26 cases from 2.1 to 2.5 gm.; and in 8 cases from 2.6 to 3.0 gm.

The hemopoietic and clinical re-

sponse to folic acid therapy is illustrated in 3 representative case histories (Cases 1, 2 and 3). Also illustrated in these case histories are: the effect of an increased intake of animal protein on the plasma proteins in Case 1; the effect of long-continued subsistence on a diet low in animal protein on the plasma proteins in Case 2; and the effect of a special protein supplement on the plasma protein levels in Case 3.

**CASE 1.** J. C., a 63 year old Cuban street vendor, was admitted to the General Calixto Garcia Hospital in November of 1945, complaining of diarrhea, weakness, and weight loss.

**Family History and Past History:** Irrelevant.

**Present Illness:** Seven months prior to his admission the patient noted for the first time a diarrhea characterized by the passing of from 3 to 4 large, yellow-colored, foul-smelling stools daily which were accompanied by pain in the rectum and abdominal cramps. Soon afterwards his tongue felt swollen and sore and he realized that hot or acid foods caused it to burn; he noticed also that it was very red, especially at the tip. At that time he consulted a physician who gave him a total of 15 cc. of liver extract intramuscularly which relieved his symptoms. After that he had several recurrences of soreness of the tongue and diarrhea which always were relieved following liver extract therapy. Four months after he first became ill and 3 months prior to his admission to the hospital, the loss of appetite and strength, the diarrhea, and the soreness of the tongue became much more pronounced than before. By this time his appetite was so poor he ate only small amounts of cornmeal, viandas (root vegetables grown in Cuba), and occasionally a glass of milk—a diet which supplied far less than the recommended allowances of nutrients. (See Fig. 1.) Within 3 months he lost 25 pounds in weight and he was so weak he spent most of the time in bed. On the advice of a friend he came to the hospital for treatment.

Physical examination showed a small, pale, undernourished man who appeared to be extremely weak. Both the skin and the mucosa were very pale and the skin had a yellowish cast. The tongue was swollen, slick, and red. The heart, lungs, and nervous system were normal.

**Laboratory Findings:** The blood values on admission were: red blood cells 1.60 million;

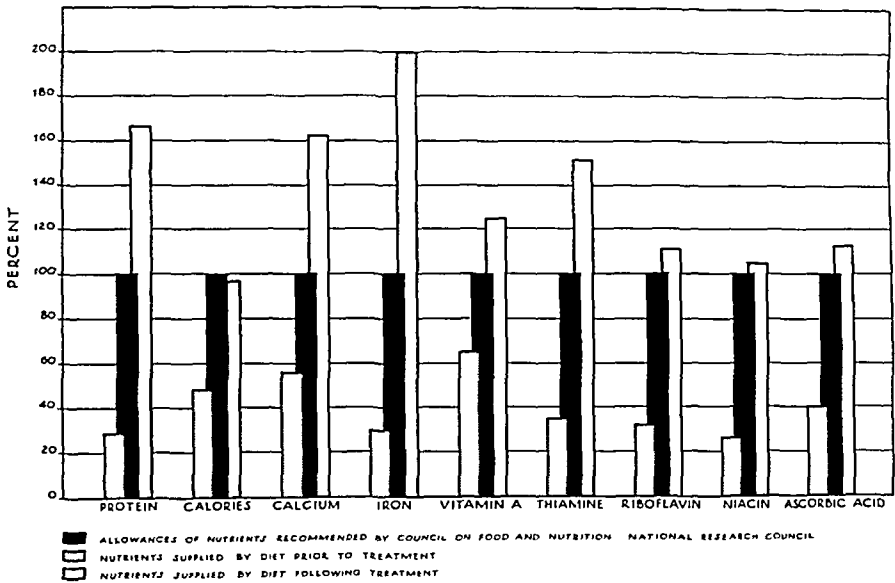


FIG. 1. CASE 1 (J. C.). Nutrients supplied by diet of patient with tropical sprue before and after folic acid therapy contrasted with the recommended allowance of nutrients.

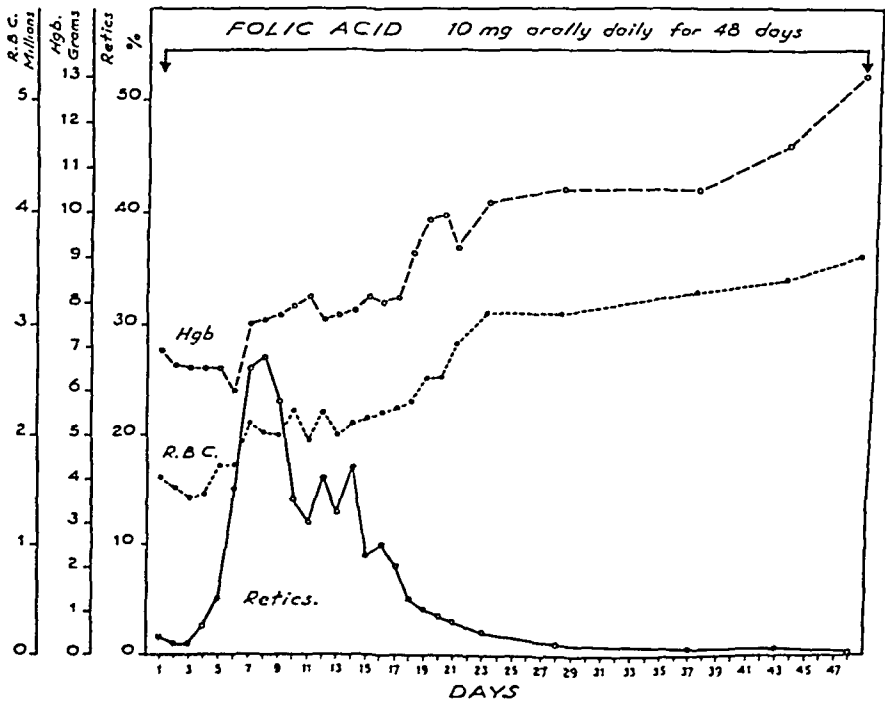


FIG. 2. CASE 1 (J. C.). Hemopoietic response to folic acid of a patient with tropical sprue.

white blood cells 5,150; hemoglobin 6.9 gm. (44%); reticulocytes 1.1%. Repeated gastric analyses showed free hydrochloric acid in the fasting specimen of the gastric juice. An oral glucose tolerance test showed a flat curve. The stools were liquid, yellow, and foamy, and contained particles of undigested food. Microscopic study revealed no ova, cysts, or parasites. Tests for occult blood gave negative results. An average of 3 plasma protein determinations showed: total protein 5.0 gm. %; albumin 2.8 gm. %; globulin 2.2 gm. %.

After the base line studies were completed, the patient was given 10 mg. of folic

improved gradually until they approached normal by the 15th day. By the time he was discharged from the hospital after 48 days on folic acid therapy, he had gained 15 pounds in weight. At this time his plasma protein levels were: total protein 5.4 gm. %; albumin 3.2 gm. %; globulin 2.2 gm. %. When he was discharged he was advised to eat a diet which included liberal amounts of meat, fish, eggs, and milk, and was asked to return at frequent intervals for follow-up studies. As can be seen in Fig. 1, his diet at home improved greatly in comparison with what it had been prior to treatment. One and one-half years after he left the hospital,

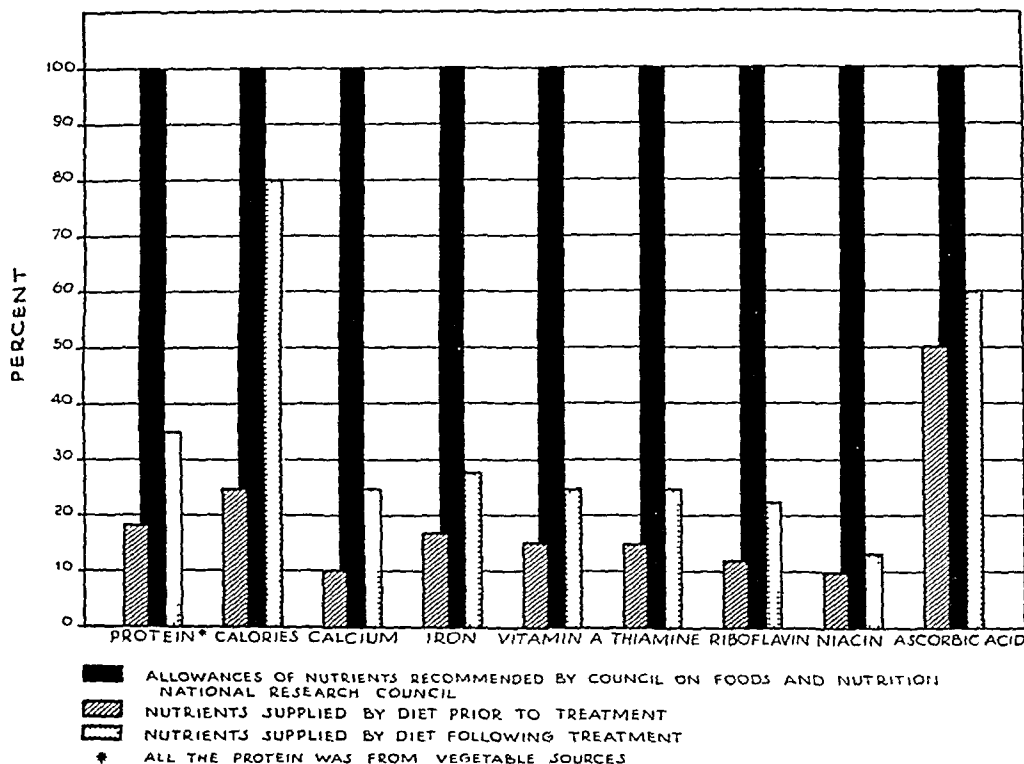


FIG. 3. CASE 2 (P. E.). Nutrients supplied by diet of patient with tropical sprue before and after folic acid therapy contrasted to recommended allowances of nutrients.

acid daily by mouth. On the 7th day of therapy the reticulocytes reached a peak of 26%. This was followed by a steady increase in red blood cells and hemoglobin and when he was discharged after 48 days on treatment, his counts were as follows: red blood cells 3.60 million; white blood cells 5,850; hemoglobin 12.7 gm. (83%) (See Fig. 2). Clinical improvement began on the 4th day of therapy with a sudden increase in strength, appetite and food intake, and a great improvement in the glossitis. The diarrhea began to subside on the 6th day and the color, consistency, and volume of the stools

his plasma protein levels were: total protein 7.2 gm. % (albumin, 4.6; globulin, 2.6).

CASE 2. P. E., a 65 year old Cuban copper mine worker was admitted to the General Calixto Garcia Hospital in November of 1945, complaining of diarrhea, loss of appetite, weakness, and weight loss.

Family History and Past History: Irrelevant.

Present Illness: Five years prior to his admission to the hospital, the patient developed diarrhea, loss of appetite, and loss of strength, and his mouth and tongue became sore. For the first time in his life he passed

2 or 3 liquid to soft, light-colored stools each day and within a week the number had increased to 8 to 10 daily and they were yellow, foul-smelling, foamy, and accompanied by severe abdominal cramping. He was given liver extract injections by his physician and following this therapy his symptoms disappeared. He remained well for 4½ years and then suddenly the diarrhea returned and he lost his appetite, strength, and body weight. His tongue became so sore he could eat nothing but soups made with viandas (root vegetables grown in Cuba), rice, coffee, and a little milk. The nutrients supplied by his diet at

involved both lower legs (see Fig. 4). There was profound abdominal distention. The heart, lungs, and nervous system appeared normal.

**Laboratory Findings:** The blood values on admission were: red blood cells 2.30 million; white blood cells 7,900; hemoglobin 8.3 gm. (54%); reticulocytes 1.0%. Repeated gastric analyses showed free hydrochloric acid in the fasting gastric contents. An oral glucose tolerance test showed a flat curve. The stools were liquid, yellow, and contained undigested particles of food. Microscopic study showed no ova, cysts, or parasites. Tests for occult blood were negative. The averages of 3

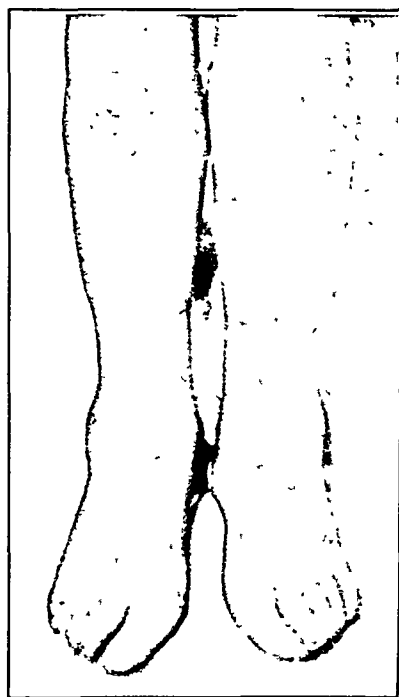


FIG. 4. CASE 2 (P. E.). Pitting edema of lower legs.

this time are shown in Fig. 3. Throughout the 6 months following he continued working every day despite extreme weakness and during this period he lost 30 pounds in weight. At the end of this time he was brought to the hospital for treatment.

Physical examination showed a small, extremely underweight man who appeared weak and desperately ill. The skin was pale, dry, and loose, and indicated loss of much subcutaneous fat. The conjunctivae, oral mucosa, and nail beds were exceedingly pale. The tongue was smooth and fiery red along the edges. Severe pitting edema in-

plasma protein determinations were: total protein 3.6 gm. % (albumin 2.4, globulin 1.2).

After the base line studies were completed, he was given 10 mg. of folic acid daily by mouth. On the 8th day the reticulocytes reached a peak of 12.5%. When he was discharged after 46 days on therapy, his counts, as can be seen in Fig. 5, were as follows: red blood cells 3.90 million; white blood cells 12,550; hemoglobin 11.0 gm. (71%); reticulocytes 0.6%. Three days after therapy was initiated, his appetite increased so that he ate all the food on his trays and

asked for more. At this time he volunteered that he felt stronger and he began walking around the ward and visiting with other patients. There was considerable improvement in the glossitis, and 2 days later it disappeared. The diarrhea began to subside on the 3rd day of therapy and at the end of 2 weeks the stools were still soft but approached normal color. When he was discharged, after 46 days on treatment, he had gained 11 pounds in weight.

CASE 3. A. M., a 66 year old Cuban school teacher, was admitted to the General Calixto Garcia Hospital in August of 1948, complaining of weakness and diarrhea.

Family History and Past History: Irrelevant.

extract gave some relief at first but gradually it seemed to become less and less effective. His appetite throughout these 8 months was very poor and his diet consisted chiefly of small amounts of rice, beans, viandas (root vegetables grow in Cuba), cornmeal, bread, sugar, and coffee. As can be seen in Fig. 6, his diet supplied only 34% of the recommended allowance of protein and all of this was from vegetable sources. One month prior to his admission to the hospital he became so weak he was forced to give up his position as a school teacher. From this time until he came to the hospital seeking treatment, he spent most of his time in bed.

Physical examination showed a well-

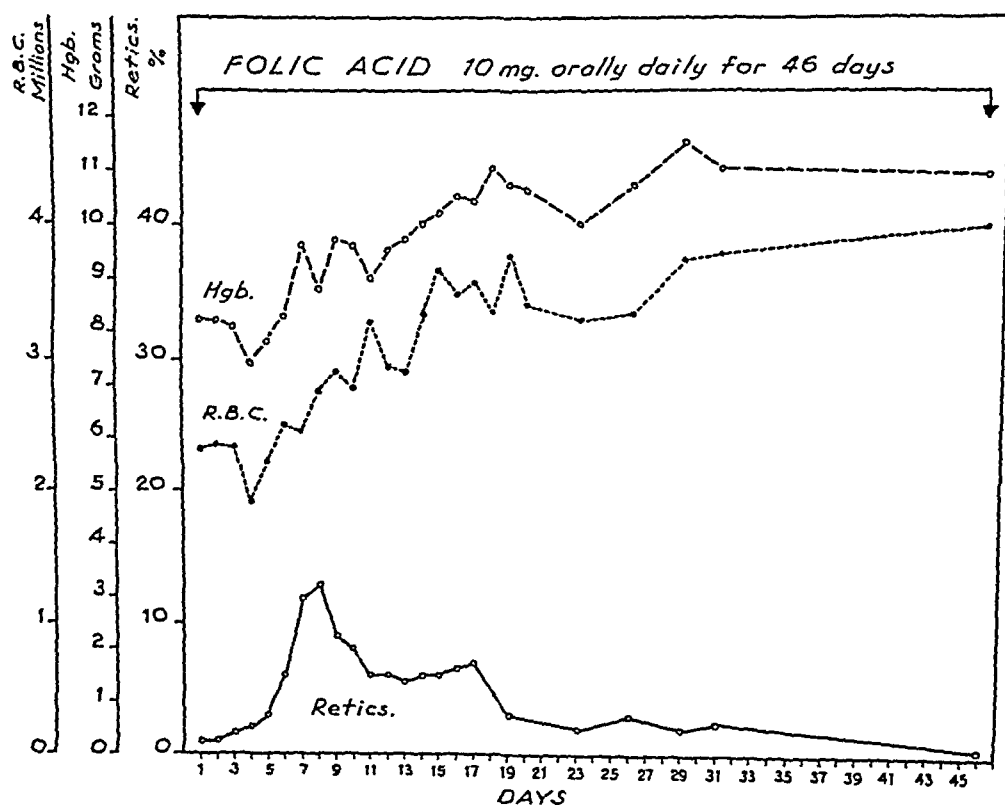


FIG. 5. CASE 2 (P. E.). Hemopoietic response of a patient with tropical sprue to folic acid.

Present Illness: Five years prior to his admission to the hospital he developed severe diarrhea, lost his appetite, and lost weight and strength. His physician prescribed injections of liver extract, and following this therapy his symptoms disappeared. During the following 4 years he had several recurrences of these symptoms which always were relieved by liver extract. Eight months prior to his admission he developed severe diarrhea consisting of from 15 to 17 watery, yellowish-green, foamy stools daily which were preceded by intestinal cramping. Liver

developed, edematous, and emaciated man, acutely and severely ill. He had dyspnea and orthopnea and was unable to walk or stand. Areas of pellagrous dermatitis were present on the dorsum of the hands, forearms, ankles, feet, and legs. The skin over the entire body was dry and inelastic. The conjunctivae, nail beds, and oral mucosa were pale. He had no teeth and his tongue was red along the border and at the tip. Pitting edema was present as high as the lower thigh.

Laboratory Findings: The blood values on



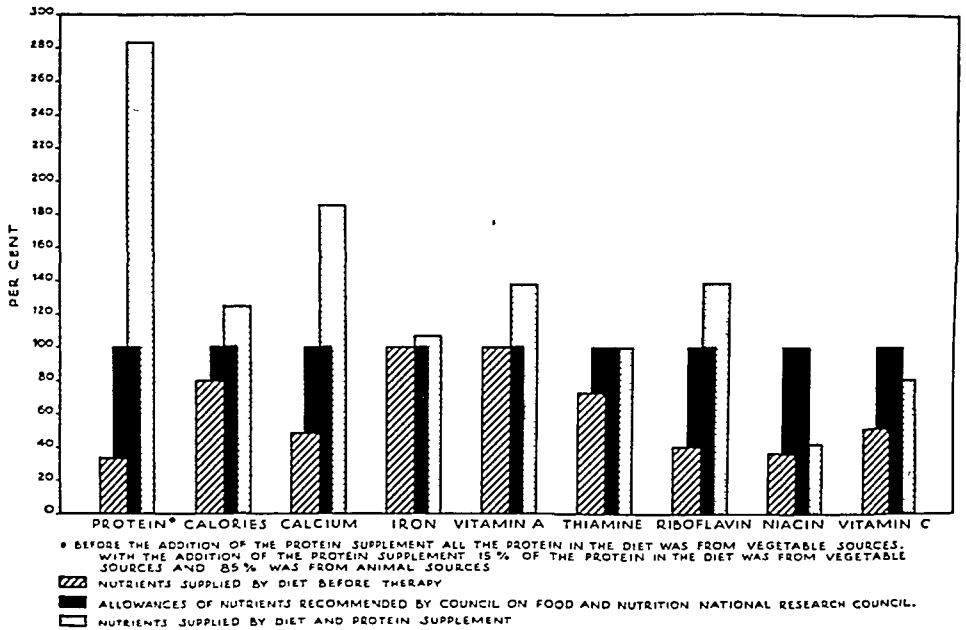


FIG. 6. CASE 3 (A. M.). Nutrients supplied by diet of patient with tropical sprue and hypoproteinemia before and after the addition of a protein supplement.

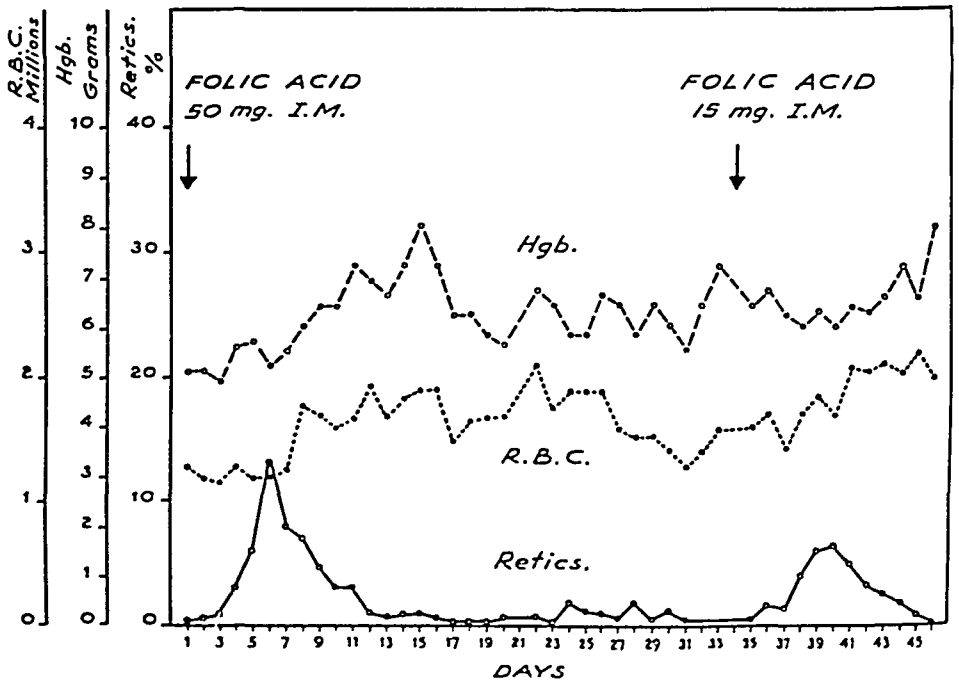


FIG. 7. CASE 3 (A. M.). Hemopoietic response of a patient with tropical sprue to folic acid.

admission were: red blood cells 1.27 million; hemoglobin 5.1 gm. (33%); reticulocytes 0.4%. Repeated gastric analyses showed free hydrochloric acid in the fasting gastric contents. An oral glucose tolerance test showed a flat curve. The stools were yellow, liquid, gaseous, foul-smelling, and voluminous, and contained particles of undigested food; microscopic study showed no ova, cysts, or parasites, and tests for occult blood were negative. The averages of 3 plasma protein determinations were: total protein 3.9; albumin 2.2; globulin 1.7 gm. %.

He was given 50 mg. of folic acid intramuscularly. Three days later his appetite improved considerably and he said he felt stronger. Six days after therapy, the diarrhea decreased from 8 to 10 liquid stools daily to from 1 to 3 partially-formed, pasty, less foul-smelling stools which were somewhat more brownish in color than they had been previously. The reticulocytes reached a peak of 13.2% on the 6th day following therapy (see Fig. 7). On the 13th day, the blood counts were: red blood cells 1.91 million; white blood cells 5,500; hemoglobin 6.9 gm. (44%); reticulocytes 1.0%. Thirty-four days after the injection of folic acid, the blood values were: red blood cells 1.60 million; white blood cells 3,150; hemoglobin 6.4 gm. (41%); reticulocytes 0.4%. By this time the volume of the stools had increased and they again became liquid, yellow, and foamy. The glossitis also reappeared. He was given 15 mg. of folic acid intramuscularly. Seven days later the reticulocyte count reached a peak of 6.4%. Eleven days later the red blood cell count was 2.20 million; white blood cells 4,200; hemoglobin 6.6 gm. (43%); reticulocytes 0.8%. The diarrhea and glossitis subsided 4 days after the injection of folic acid. He remained very weak, however, and his protein levels were essentially the same as they were at the time of his admission to the hospital.

The protein deficiency was so severe in this patient that it was decided to give him a special protein supplement. During the course of 24 hours he was given in addition to the ward diet a supplement, totaling 200 gm., of "Tomac" (a mixture of calcium, lactalbumin, food yeast, sugar, dextrin, etc., with a protein content of 70%) mixed with 1,000 cc. of whole milk, thus adding to his daily food intake 175 gm. of protein and 1,316 calories. (See Fig. 6, which shows the nutrients supplied by his diet before and after the addition of the protein supplement.) The patient tolerated the supplement well and his condition improved rapidly. Within 10 days he had no clinical evidence

of edema. He appeared very emaciated at this time. The protein supplement was continued for an additional 2 weeks and he continued steadily to gain weight and strength. During the 3rd week he was able to sit up in bed and began to walk with support from others. During the 4th week on the protein supplement he could walk unaided. He developed a sense of well-being and wished to return to his work. The 5th week after initiating the protein supplement he was able to walk to his home, which was a short distance away. By this time his plasma protein levels had increased to: total protein 5.2 gm. % (albumin, 3.6; globulin 1.6).

**Summary and Conclusions.** Of 155 cases of severe tropical sprue in Cuba who gave a history of eating a diet which contained little or no animal protein, 121 were selected for study. Of these patients, 80 had a total plasma protein of 6.0 gm. % or less. Repeated determinations showed that the lowest total protein was 3.2 gm. %.

Despite the low protein levels of the blood and the presence of clinical edema in 81 patients, a hemopoietic response to folic acid occurred in each case of tropical sprue. In 20 cases there was a transitory but significant increase in the edema associated with this hemopoietic response.

These patients regenerated red blood cells and hemoglobin despite their subsistence on a diet devoid of animal protein. The authors gained the distinct clinical impression that on this diet some of the patients did not have as rapid a hemopoietic response as did other patients on a diet higher in protein.

It is remarkable, however, that the blood regenerated despite the fact that these patients remained on a diet restricted in animal protein throughout the time they were in the hospital and that in many cases the plasma protein decreased. These patients improved greatly in health, strength, and vigor and many of them were able to resume work. Nevertheless, in treating such

patients, the authors strongly recommend the use of high protein diets along with the antianemic therapy *per se*, as it is obvious that the body cannot make amino acids from folic acid, and that proteins of good quality (such as milk, meat, and eggs) also are needed for full rehabilitation.

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# EFFECTS OF VASODILATOR DRUGS AND OTHER PROCEDURES ON DIGITAL CUTANEOUS BLOOD FLOW, CARDIAC OUTPUT, BLOOD PRESSURE, PULSE RATE, BODY TEMPERATURE, AND METABOLIC RATE

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DRUGS used to dilate cutaneous blood vessels should, ideally, be selective in their action. If they cause dilatation of vessels in other areas simultaneously, 3 disadvantageous phenomena may occur: 1, If the vasodilatation elsewhere is considerable it tends to divert blood from the skin. 2, General vasodilatation tends to reduce blood pressure; this in turn gives rise to vasoconstrictor reflexes which tend to counteract the desired cutaneous vasodilatation<sup>17</sup>. 3, If other vascular beds are dilated, an increase in cardiac output per minute will probably occur, and this might be undesirable in cardiac disease, which exists in many patients with peripheral vascular disease. Consequently, the following studies were made in an attempt to evaluate the cutaneous selectivity of certain vasodilator therapeutic procedures. The criterion for increase in the cutaneous circulation which was used was an increased digital skin temperature in the presence of controlled environmental conditions. The criteria for an increase in the circulation elsewhere than in the skin, designated in this paper as "splanchnic circulation", were increased pulse rate, decreased

blood pressure, or increased cardiac output per minute (determined by ballistocardiogram).

Measurements of body temperature (oral and rectal) and of metabolism were made in order to learn whether, as in the case of ingestion of food, cutaneous vasodilatation in response to drugs results from an increase in body temperature and in metabolism. When this was found not to be so, in the case of several groups of subjects receiving different drugs, the measurements of metabolism were abandoned. The measurements of body temperature, however, were continued, because increases in cutaneous circulation, caused by various drugs, lowered body temperature in proportion to these increases. Measurements of body temperature afford further evidence of the effectiveness of drugs as cutaneous vasodilators.

**Subjects, Materials and Methods.** The subjects chosen for the experiments were healthy adults of both sexes between 16 and 42 years of age. They reported for the studies without having had food for from 6 to 12 hours. They reclined, scantily clad in an examining gown and a sheet, on a ballistocardiographic table in a thermoregulated room. In most instances the room was kept at a  $22 \pm 1^\circ \text{C}$ .

(see Table 1), since it was found that this temperature induced a satisfactory but not excessive peripheral vasoconstriction within a reasonable time. Before measuring the effects of a drug or other procedure there was a control period sufficient to induce partial or complete peripheral cutaneous vasoconstriction and to establish nearly constant values for all the phenomena measured.

Each drug or other procedure was evaluated in a series of 3 to 11 instances, the shorter series being thought to be adequate when previous data supported them<sup>17</sup>. Only one procedure was carried out on any one subject on any one day. A control series of 6 subjects was studied, using no vasodilator procedure. The following drugs and other vasodilator procedures were used: heat to body, food, alcohol, 2 benzyl 4, 5-imidazoline HCl, acetyl-beta-methyl choline chloride, tetraethylammonium chloride, and nicotinic acid.

Pulse rates were taken from the radial artery and the ballistocardiographic tracings. Blood pressure was measured by the Riva-Rocci method. Cardiac output per minute was estimated by a ballistocardiograph of the Starr type<sup>24</sup> and tabulated as cc. per kg. per minute. Either mouth temperature or rectal temperature or both were regularly recorded. Skin temperature was measured by thermocouples held by adhesive tape to tips of fingers and toes. Digital blood flow was calculated from these measurements by a relationship previously established<sup>18</sup>, affording semi-quantitative data (cc. per 100 cc. of digit per minute) on predominantly cutaneous digital blood flow. Mouth temperature was measured directly by a clinical thermometer left under the tongue for at least 5 minutes. Rectal temperature was measured by indwelling thermocouples. Metabolic rate was measured by means of a standard Benedict-Roth apparatus<sup>2</sup>.

The following changes were taken to be significant: pulse rate of 10 beats or more per min., blood pressure of 10 mm. Hg., cardiac output of 10 cc. per kg. per min., and blood flow of 2 cc. per 100 cc. of digit per min. in the lower ranges of flow (0 to 10 per 100 cc. of digit per min.) and of 5 to 20 cc. in the higher ranges of flow (10 to 100 cc. per 100 cc. of digit per min.)<sup>18</sup>. Blood flow of 1 or 2 cc. per 100 cc. of tissue per min. represents minimal blood flow and figures of 50 cc. or more can be considered as maximal blood flow.

**Results. Controls.** Six normal subjects were used as controls (Table 1). Studies of pulse rate, blood pressure,

cardiac output per minute, digital cutaneous blood flow, and rectal temperature were made in the manner described above. After each preliminary period during which all measurements were becoming relatively constant, a needle was inserted momentarily deep into the skin without introducing any drug. Pulse rate, blood pressure and cardiac output per minute were not affected significantly in any case. In no instance was there any increase in cutaneous blood flow in fingers or toes. In the fingers there were 2 instances in which there was an insignificant change, and in 4 there were "significant" decreases from low levels to minimal after 2, 12, 35, and 26 minutes. In the toes there was 1 instance in which there was an insignificant change, and in 5 there were slight but "significant" decreases in cutaneous blood flow from low levels after 18, 50, 30, 50, and 69 minutes. Rectal temperatures decreased in all instances during the preliminary period (average 0.1° C.). The decrease in rectal temperature was rapid until cutaneous vasoconstriction occurred. After vasoconstriction was approximately complete with a "minimal" cutaneous flow of digital blood, rectal temperature varied little, and no significant changes occurred as a result of the introduction of a needle into the skin. Basal metabolism was not studied in this group of controls.

**Heat.** In 1942 our preliminary experiments<sup>17</sup> suggested that body warming increased digital cutaneous blood flow with little change in cardiac output per minute. The present studies confirm this. Body warming was induced in 9 individuals. Two heating pads were applied to the trunk, and 3 blankets to all but the head, 1 arm, and 1 foot, which were left uncovered. These circumstances are much the same as those used by Lewis and

Pickering<sup>15</sup>, and Gibbon and Landis<sup>11</sup>, in relieving vasomotor tone.

There were slight increases in pulse rate, in blood pressure, in cardiac output per minute, and in metabolic rate. Conspicuous reflex vasodilatation occurred promptly in the fingers and later, if at all, in the toes. The effect was usually maximal within an hour. Sweating was usually profuse. Body temperature increased by an average of  $0.1^{\circ}\text{C}$ .

*Food.* Meals of 200 to 800 calories were administered to 7 subjects over periods of 10 to 15 minutes. These subjects were kept in the recumbent position while eating. The contents of the meals were: protein 5 gm. to 40 gm., fat negligible to 240 gm. and carbohydrate 40 gm. to 400 gm. The effects of high and of low caloric meals were so similar that they are reported together.

Pulse, blood pressure, cardiac output per minute and cutaneous blood flow through the fingers tended to increase. Unlike the experiments in 1942<sup>17</sup> there were no significant increases in cutaneous blood flow through the toes. We have no explanation for this. There was no visible sweating. The average increase in body temperature was  $0.1^{\circ}\text{C}$ ., about the same as in the group subjected to body warming. In all but one instance there was a moderate increase of the metabolic rate.

These results are in general agreement with those of Roth and Sheard<sup>20</sup> who made observations of the effect of 1 meal, or 2 to 4 meals in close succession, on the pulse, blood pressure, body temperature, metabolic rate, and changes in digital temperature.

*Ethyl alcohol.* Grollman<sup>12</sup> demonstrated that 35 cc. of ethyl alcohol taken by mouth causes a slight increase in pulse rate, with an average of 4 beats per minute beginning in 10 to 30 minutes; and a slight rise in systolic and diastolic blood pressure, averaging

10% of basal values. The duration of the maximal effects in these cases was generally limited to within 10 to 15 minutes. He concluded that "the magnitude of this response is so small, however, that one cannot infer that alcohol is a stimulant to the circulation." He stated that the relatively slight effect of alcohol on the cardiac output per minute would indicate that "the vasodilatation is probably limited to the peripheral vessels." Cook and Brown<sup>8</sup> in 1932 had measured in skin temperatures in the fingers and toes following ingestion of 0.5 cc. of alcohol per kg. of body weight. Their studies were made at environmental temperatures of  $24$  to  $26^{\circ}\text{C}$ ., and they demonstrated increases in skin temperatures of all subjects. Our previous observations<sup>17</sup> had shown a considerable increase in the digital cutaneous blood flow in response to oral alcohol, with little change in pulse rate, blood pressure, or cardiac output per minute. Cutaneous blood flow increased conspicuously in fingers, but larger doses were required to cause striking changes in the toes. We have found no other reports of simultaneous measurements of cardiac output per minute and digital cutaneous blood flow.

In the present experiments, 60 to 150 cc. of whiskey, with an alcoholic content of 24 to 60 cc., were diluted and given to each of 5 subjects. In 1 other instance a subject was given 600 cc. of 5% alcohol intravenously within 120 minutes, as fast as the subject could tolerate the pain in the vein receiving it. No vasodilatation resulted. This was followed by 60 cc. of whiskey by mouth, and vasodilatation then occurred. In none of the 5 experiments was there more than mild euphoria. No significant change in pulse rate, blood pressure, or cardiac output per minute resulted. In every case large increases in cutaneous blood flow resulted in the fingers. In all but 1

TABLE I  
PROCEDURES ON  
BLOOD OUTPUT, BLOOD  
PRESSURE, AND OTHER  
CARDIAC AND  
RESPIRATORY  
FUNCTIONS

| TABLE 1<br>EFFECTS OF VASODILATOR DRUGS AND OTHER PROCEDURES ON<br>DIGITAL CUTANEOUS BLOOD FLOW, CARDIAC OUTPUT, BLOOD<br>PRESSURE, PULSE RATE, BODY TEMPERATURE, AND METABOLIC RATE. |       |      |      |            |                |           |             |                |                |               |             |             |                              |             |             |             |                 |    |                |       |
|---|-------|------|------|------------|----------------|-----------|-------------|----------------|----------------|---------------|-------------|-------------|------------------------------|-------------|-------------|-------------|-----------------|----|----------------|-------|
| SUBJECT   | DATE  | TIME | TEMP | PULSE RATE | BLOOD PRESSURE |           |             |                | CARDIAC OUTPUT |               |             |             | DIGITAL CUTANEOUS BLOOD FLOW |             |             |             | CHANGES INDUCED |    |                |       |
|   |       |      |      |            | Before         |           | Max. Change |                | Before         |               | Max. Change |             | Before                       |             | Max. Change |             | BP              | C  | T <sub>a</sub> | B M R |
|   |       |      |      |            | Systolic       | Diastolic | Mean        | Pulse Pressure | Cardiac Output | Stroke Volume | Time        | Max. Change | Before                       | Max. Change | Time        | Max. Change |                 |    |                |       |
| CONTROLS  |       |      |      |            |                |           |             |                |                |               |             |             |                              |             |             |             |                 |    |                |       |
| 1   | 12-17 | 23   | 35   | 22.0 ± 0.2 | 100 Cal        | 53        | 72          | 67             | 51             | 103/117/70    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 2   | 12-17 | 25   | 34   | 22.4 ± 0.3 | 340 Cal        | 68        | 78          | 10             | 15             | 115/119/78    | 15          | 20          | 15                           | 20          | 15          | 20          | 15              | 20 |                |       |
| 3   | 12-17 | 27   | 34   | 22.4 ± 0.2 | 400 Cal        | 140       | 76          | 48             | 50             | 100/118/70    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 4   | 12-17 | 29   | 34   | 22.4 ± 0.1 | 400 Cal        | 170       | 62          | 15             | 40             | 100/110/70    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 5   | 12-17 | 31   | 34   | 22.4 ± 0.3 | 720 Cal        | 75        | 88          | 20             | 65             | 120/110/65    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 6   | 12-17 | 33   | 34   | 22.4 ± 0.5 | 720 Cal        | 140       | 60          | 51             | 51             | 114/122/80    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 7   | 12-17 | 35   | 34   | 22.4 ± 0.2 | 720 Cal        | 56        | 63          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 8   | 12-17 | 37   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 9   | 12-17 | 39   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 10  | 12-17 | 41   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 11  | 12-17 | 43   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 12  | 12-17 | 45   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 13  | 12-17 | 47   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 14  | 12-17 | 49   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 15  | 12-17 | 51   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 16  | 12-17 | 53   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 17  | 12-17 | 55   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 18  | 12-17 | 57   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 19  | 12-17 | 59   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| 20  | 12-17 | 61   | 34   | 22.4 ± 0.2 | 720 Cal        | 11        | 11          | 11             | 11             | 120/120/76    | 10          | 15          | 10                           | 15          | 10          | 15          | 10              | 15 |                |       |
| Aver. 22.4  |       |      |      |            |                |           |             |                |                |               |             |             |                              |             |             |             |                 |    |                |       |

|               |         |       |       |       |          |       |       |       |       |       |        |        |       |       |          |          |       |       |    |   |       |     |     |       |       |       |       |       |     |         |     |     |     |       |        |
|---------------|---------|-------|-------|-------|----------|-------|-------|-------|-------|-------|--------|--------|-------|-------|----------|----------|-------|-------|----|---|-------|-----|-----|-------|-------|-------|-------|-------|-----|---------|-----|-----|-----|-------|--------|
| A. K.         | 4-7-47  | 21 M  | 74.5  | 68    | 21.0±0.5 | ..... | 52    | 72    | 70    | 85+   | 98/72  | 102/72 | CNS   | CNS   | 56 57 45 | 65 60 55 | 65    | 20+   | 2  | 1 | 95    | 30  | 60  | 80    | 77+   | 42+   | 0     | -5    | +20 | +4/0    | +10 | +93 | +23 | -5    | +0.3 O |
| L. S.         | 4-8-47  | 20 M  | 70.5  | 72    | 19.5±0.5 | ..... | 49    | 63    | 95    | 110+  | 125/75 | 120/80 | CNS   | CNS   | 49 71 44 | 62 69 54 | 85    | 55+   | 1  | 1 | 72    | 1   | 130 | CNS   | 80+   | CNS   | -10   | +9    | +14 | -5/+5   | +10 | +71 | 0   | +19   | ±0.0 O |
| P. B.         | 4-9-47  | 21 M  | 66.5  | 67    | 21.7±0.7 | ..... | 61    | 68    | CNS   | CNS   | 112/68 | 118/76 | CNS   | CNS   | 62 54 51 | 58 51 53 | CNS   | CNS   | 1  | 1 | 40    | 1   | 92  | CNS   | 65+   | CNS   | +6    | 0     | +7  | +6/+8   | +2  | +39 | 0   | -6    | +0.2 O |
| S. Y.         | 4-10-47 | 21 M  | 70.5  | 71    | 20.8±1.0 | ..... | 66    | 78    | 60    | 33+   | 124/70 | 134/70 | 82    | 10+   | 66 73 61 | 71 70 63 | CNS   | CNS   | 2  | 1 | 100   | CNS | 67  | CNS   | 90+   | CNS   | ..... | ..... | +12 | +10/0   | +2  | +98 | +1  | ..... | +0.2 O |
| E. F.         | 5-12-47 | 21 M  | 77.5  | 75    | 23.0±1.0 | ..... | 68    | 88    | 43    | 38+   | 135/90 | 110/75 | 27    | 78+   | 59 65 50 | 68 67 59 | CNS   | CNS   | 1  | 1 | 53    | 1   | 71  | CNS   | 59+   | CNS   | +5    | +12   | +20 | -25/-15 | +9  | +52 | 0   | +7    | +0.2 O |
| L. T.         | 4-12-48 | 24 M  | 50    | 65    | 24.0±0.5 | ..... | 68    | 76    | CNS   | CNS   | 110/70 | 130/90 | 48    | 66+   | 68 42 48 | 69 46 54 | CNS   | CNS   | 80 | 1 | 100   | 5   | 12  | 67    | 724+  | 40+   | ..... | ..... | +8  | +20/+20 | +6  | +40 | +1  | ..... | -0.2 R |
| R. C.         | 4-14-48 | 22 M  | 84    | 72    | 21.0±1.0 | ..... | 75    | 80    | CNS   | CNS   | 119/82 | 125/85 | CNS   | CNS   | 75 59 53 | 80 58 50 | CNS   | CNS   | 30 | 1 | 100   | 1   | 22  | CNS   | 60+   | CNS   | ..... | ..... | +5  | +6/+3   | +3  | +70 | 0   | ..... | +0.3 R |
| R. P.         | 4-13-48 | 28 M  | 77.5  | 71    | 23.0±1.0 | ..... | 68    | 76    | CNS   | CNS   | 110/70 | 124/70 | 40    | 24+   | 68 53 47 | 70 59 53 | CNS   | CNS   | 3  | 1 | 100   | 26  | 38  | 38    | 50+   | 43+   | ..... | ..... | +8  | +14/0   | +6  | +97 | +25 | ..... | +0.4 R |
| J. L.         | 4-15-48 | 23 M  | 67    | 71    | 21.0±1.2 | ..... | 68    | 72    | CNS   | CNS   | 118/75 | 119/79 | CNS   | CNS   | 67 50 56 | 69 57 58 | CNS   | CNS   | 1  | 1 | 39    | 1   | 50  | CNS   | 33+   | CNS   | ..... | ..... | +4  | +1/+1   | +2  | +38 | 0   | ..... | -0.1 R |
| Aver-<br>ages | .....   | ..... | ..... | ..... | 21.7     | ..... | ..... | ..... | ..... | ..... | .....  | .....  | ..... | ..... | 63 59 51 | 68 60 56 | ..... | ..... | 11 | 1 | ..... | 8   | 60  | ..... | ..... | ..... | 0     | +4    | +11 | +3/+3   | +6  | +65 | +7  | +4    | +0.1   |

## 2-BENZYL-4, 5-IMIDAZOLINE (PRISCOL) (INTRAVENOUSLY)

|               |         |       |       |       |          |          |       |       |     |       |            |             |     |       |          |           |       |       |   |   |    |    |     |       |       |       |       |       |         |         |     |     |       |        |        |
|---------------|---------|-------|-------|-------|----------|----------|-------|-------|-----|-------|------------|-------------|-----|-------|----------|-----------|-------|-------|---|---|----|----|-----|-------|-------|-------|-------|-------|---------|---------|-----|-----|-------|--------|--------|
| O. H.         | 7-8-47  | 30 M  | 77.5  | 72    | 22.5±0.5 | 30 mgms. | 62    | 71    | CNS | CNS   | 110/<br>70 | 104/<br>62  | CNS | CNS   | 62 69 51 | 70 59 52  | CNS   | CNS   | 3 | 2 | 13 | 5  | 5   | 7     | 12    | 24    | -12   | -20   | +9      | -6/-8   | +1  | +10 | +3    | -8     | -0.4 R |
| H. M.         | 7-11-47 | 43 M  | 86.5  | 75    | 23.5±0.5 | 40 mgms. | 60    | 72    | 2   | ..... | 118/<br>70 | 114/<br>70  | CNS | CNS   | 62 78 56 | 65 76 57  | CNS   | CNS   | 2 | 1 | 4  | 7  | 64  | 44    | 38    | 110+  | ..... | ..... | +12     | -4/0    | +1  | +2  | +6    | .....  | -0.4 R |
| E. M.         | 7-15-47 | 41 F  | 54    | 63    | 24.0±0.6 | 15 mgms. | 64    | 130   | 2   | 15    | 110/<br>72 | 130/<br>80  | 10  | 25    | 63 45 52 | 80 45 67  | 5     | 10    | 1 | 2 | 17 | 4  | 86  | 85+   | 20    | ..... | ..... | ..... | +60     | +20/+8  | +15 | +16 | +2    | .....  | -0.1 O |
| J. K.         | 7-17-47 | 29 M  | 76.5  | 72    | 24.0±0.5 | 40 mgms. | 55    | 68    | 20  | ..... | 116/<br>80 | 127/<br>78  | 25  | 40    | 51 64 43 | 62 59 48  | CNS   | CNS   | 3 | 2 | 25 | 5  | 30  | 20    | 45+   | 45+   | +3    | +2    | +12     | +11/-2  | +5  | +22 | +3    | -1     | -0.1 O |
| W. B.         | 4-21-48 | 28 M  | 95.5  | 73    | 21.5±1.5 | 50 mgms. | 62    | 78    | 22  | 30    | 108/<br>76 | 130/<br>98  | 75  | 104   | 62 63 41 | 64 52 34  | 65    | 94    | 5 | 4 | 29 | 13 | 90  | 75    | 53    | 80    | ..... | ..... | +16     | +52/+22 | -7  | +24 | +9    | .....  | -0.3 R |
| R. P.         | 4-22-48 | 21 M  | 68    | 72    | 20.5±1.2 | 40 mgms. | 80    | 140   | 3   | 20    | 134/<br>78 | 154/<br>78  | 3   | 95    | 78 51 58 | 106 50 78 | 3     | 12    | 1 | 1 | 7  | 2  | 95  | CNS   | 95    | CNS   | ..... | ..... | +60     | +20/0   | +20 | +6  | +1    | .....  | +0.3 R |
| D. S.         | 4-20-48 | 21 M  | 84.0  | 75    | 23.0±2.0 | 40 mgms. | 65    | 98    | 4   | 82    | 126/<br>90 | 162/<br>104 | 57  | 75+   | 65 70 54 | 70 50 41  | 3     | ..... | 1 | 1 | 7  | 1  | 92  | CNS   | 81+   | CNS   | ..... | ..... | +33     | +36/+14 | -13 | +6  | 0     | .....  | -0.4 R |
| M. A.         | 5-5-48  | 21 M  | 75    | 70    | 22.4±1.4 | 50 mgms. | 66    | 99    | 2   | 59    | 112/<br>80 | 132/<br>96  | 35  | 60+   | 66 59 53 | 66 50 65  | 5     | ..... | 1 | 1 | 1  | 3  | CNS | 43    | CNS   | 9     | ..... | +33   | +20/+16 | +12     | 0   | +2  | ..... | -0.2 R |        |
| J. B.         | 3-23-48 | 20 M  | 66.5  | 72    | 21.0±0.5 | 40 mgms. | 84    | 120   | 2   | 19    | 128/<br>66 | 145/<br>90  | 40  | 58+   | 84 53 68 | 78 50 59  | 49    | 49+   | 6 | 2 | 52 | 2  | 9   | CNS   | 34    | CNS   | ..... | ..... | +36     | +17/+24 | -9  | +46 | 0     | .....  | -0.2 O |
| Aver-<br>ages | .....   | ..... | ..... | ..... | 22.5     | .....    | ..... | ..... | 8   | 38    | .....      | .....       | 36  | ..... | 66 61 53 | 77 55 56  | ..... | ..... | 3 | 2 | 17 | 5  | 59  | ..... | ..... | ..... | ..... | ..... | +31     | +18/+8  | +3  | +15 | +3    | -5     | -0.2   |



Continued

[illegible]

## ETHYL ALCOHOL (ORALLY)\*\*

| I. M.     | 6-10-47 | 43 M  | 86.5  | 75    | 23.0±1.0 | 150 cc. | 60    | CNS   | 112/72 | CNS   | 59/88 | 60 | 58 | 88 | 59 | CNS | 1     | 43 | 4  | 77  | 110 | 60+  | 10+   | +11   | +35   | 0  | 0/0   | -1 | +42 | +3  | +24   | -0.4 R |
|-----------|---------|-------|-------|-------|----------|---------|-------|-------|--------|-------|-------|----|----|----|----|-----|-------|----|----|-----|-----|------|-------|-------|-------|----|-------|----|-----|-----|-------|--------|
| I. M.     | 6-12-47 | 43 M  | 86.5  | 75    | 23.2±0.8 | 60 cc.* | 72    | CNS   | 114/81 | CNS   | 63/87 | 63 | 64 | 82 | 60 | CNS | 1     | 55 | 17 | 140 | 160 | 54+  | 39+   | +28   | +20   | -4 | +4/-8 | -3 | +54 | +16 | -8    | -0.5 R |
| O. H.     | 6-27-47 | 36 M  | 77.5  | 72    | 22.5±0.5 | 150 cc. | 60    | CNS   | 110/70 | CNS   | 60/65 | 49 | 60 | 62 | 47 | CNS | 1     | 40 | 2  | 55  | CNS | 80   | CNS   | ..... | ..... | 0  | 0/0   | -2 | +39 | +1  | ..... | -0.8 R |
| E. D.     | 7-3-47  | 24 F  | 80.5  | 70    | 24.5±0.5 | 60 cc.  | 75    | CNS   | 106/66 | CNS   | 75/48 | 58 | 68 | 52 | 57 | CNS | 2     | 15 | 7  | 30  | 45  | 43+  | 35+   | +1    | +20   | -7 | 0/0   | -1 | +13 | +5  | +19   | -0.4 O |
| P. R.     | 7-22-48 | 29 M  | 66.5  | 70    | 21.5±1.5 | 120 cc. | 72    | CNS   | 110/68 | CNS   | 72/52 | 57 | 63 | 51 | 49 | CNS | 15    | 56 | 1  | 126 | 40  | 140+ | 146+  | ..... | ..... | -6 | +6/+4 | -8 | +41 | -4  | ..... | -0.2 R |
| Aver-ages | .....   | ..... | ..... | ..... | 22.9     | .....   | ..... | ..... | .....  | ..... | 66    | 68 | 58 | 63 | 67 | 54  | ..... | 4  | 2  | 42  | 86  | 89   | ..... | +12   | +25   | -3 | +2/-1 | -3 | +38 | +4  | +12   | -0.5   |

## NIACIN (ORALLY)

| NIACIN (ORALLY) |         |       |       |       |          |           |       |       |        |         |       |       |       |       |       |       |       |       |       |       |    |    |    |    |     |       |       |       |       |       |       |         |       |     |       |        |        |
|-----------------|---------|-------|-------|-------|----------|-----------|-------|-------|--------|---------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|----|----|----|----|-----|-------|-------|-------|-------|-------|-------|---------|-------|-----|-------|--------|--------|
| D. L.           | 3-10-48 | 29 M  | 72.5  | 70    | 21.0±1.0 | 100 mgms. | 60    | CNS   | 108/80 | 100/64  | 39    | ..... | 60    | 54    | 44    | 68    | 48    | 45    | CNS   | CNS   | 11 | 5  | 1  | 1  | 39  | 15    | 60+   | 60+   | ..... | ..... | +8    | -8/-16  | +1    | -10 | -4    | .....  | -0.5 O |
| C. N.           | 5-11-48 | 29 M  | 72.5  | 72    | 24.2±0.7 | 100 mgms. | 54    | CNS   | 108/74 | 100/78  | CNS   | 54    | 68    | 51    | 56    | 68    | 53    | CNS   | CNS   | 55    | 10 | 36 | 2  | 51 | 51  | ..... | 40+   | ..... | ..... | +6    | -8/+1 | +2      | -19   | -8  | ..... | +0.3 R |        |
| J. F.           | 5-12-48 | 20 M  | 68    | 66    | 23.5±1.0 | 100 mgms. | 52    | CNS   | 128/78 | 132/80  | CNS   | CNS   | 52    | 61    | 47    | 55    | 63    | 51    | CNS   | CNS   | 19 | 1  | 2  | 1  | 66  | CNS   | 33+   | CNS   | ..... | ..... | +3    | +4/+2   | +4    | -17 | 0     | .....  | +0.1 R |
| H. G.           | 5-17-48 | 21 M  | 79.5  | 69    | 21.2±1.2 | 100 mgms. | 72    | CNS   | 124/70 | 118/72  | CNS   | CNS   | 72    | 52    | 46    | 64    | 49    | 39    | CNS   | CNS   | 60 | 3  | 33 | 2  | 81  | CNS   | ..... | CNS   | ..... | ..... | -8    | -6/+2   | -7    | -27 | -1    | .....  | +0.2 R |
| G. T.           | 5-6-48  | 20 M  | 72.5  | 71    | 22.0±1.5 | 50 mgms.  | 70    | CNS   | 122/88 | 138/100 | 36    | ..... | 70    | 53    | 51    | 68    | 55    | 51    | CNS   | CNS   | 30 | 1  | 21 | 1  | 46  | CNS   | 17+   | CNS   | ..... | ..... | -8    | +16/+12 | 0     | -9  | 0     | .....  | +0.1 R |
| C. F.           | 5-10-48 | 20 M  | 72.5  | 70    | 22.0±1.1 | 70 mgms.  | 60    | CNS   | 135/80 | 130/78  | CNS   | CNS   | 68    | 65    | 57    | 60    | 59    | 45    | 00    | 40+   | 1  | 4  | 1  | 49 | CNS | 21    | CNS   | ..... | ..... | -8    | -5/-2 | -12     | +3    | 0   | ..... | +0.2 R |        |
| A. F.           | 7-19-48 | 16 F  | 62    | 68    | 22.0±1.8 | 75 mgms.  | 63    | CNS   | 114/70 | 120/74  | CNS   | CNS   | ..... | ..... | ..... | ..... | ..... | ..... | ..... | ..... | 19 | 3  | 3  | 2  | 78  | CNS   | 75+   | CNS   | ..... | ..... | +5    | +6/+4   | ..... | -16 | -1    | .....  | +0.5 O |
| D. L.           | 7-21-48 | 30 M  | 72.5  | 70    | 21.0±1.0 | 50 mgms.  | 60    | CNS   | 120/80 | 115/78  | CNS   | CNS   | 56    | 54    | 42    | 56    | 50    | 38    | CNS   | CNS   | 13 | 6  | 1  | 1  | 91  | 91    | 70+   | 70+   | ..... | ..... | -2    | -5/0    | -4    | -12 | -5    | .....  | -0.2 O |
| Aver-ages       | .....   | ..... | ..... | ..... | 22.2     | .....     | ..... | ..... | .....  | .....   | ..... | ..... | 62    | 58    | 48    | 61    | 56    | 46    | ..... | ..... | 26 | 4  | 13 | 1  | 63  | ..... | ..... | ..... | ..... | -1    | -1/+1 | -2      | -13   | -2  | ..... | +0.1   |        |

All times in minutes.

CNS = change not significant

O = oral temperature

R = rectal temperature

+ = change still apparent at termination of experiment

..... = determination not made

\* = 600 c.c. 5% alcohol given I.V. along with this

\*\* = Dosage recorded in c.c. 80 proof whiskey

SV = Stroke vol., cc/beat

CO = Cardiac output, cc/kg/min



ously. Starr<sup>23</sup> observed an increase in cardiac output per minute resulting from subcutaneous injections of methacholine chloride ("mecholy")-acetyl-beta-methyl choline chloride) in doses of 2 to 6 mg. We<sup>17</sup> have reported the effect of such doses on digital cutaneous blood flow in 6 instances. As in neither report were simultaneous measurements of cardiac output per minute and peripheral blood flow made, we have included a study of 3 subjects. The results confirmed the previous observations. The changes were rapid and transient. In each instance methacholine chloride resulted in a conspicuous increase in pulse rate, a decrease in systolic blood pressure, and an increase in cardiac output per minute. There was no significant change in digital cutaneous blood flow or in body temperature. Metabolism was not measured.

• *Tetraethylammonium chloride, intravenously.* Tetraethylammonium chloride (Etamon) was administered intravenously in doses varying from 200 to 500 mg. at the rate of 200 mg. per minute to 11 subjects.

The prompt, conspicuous, transient changes were: increase in pulse rate, decrease in blood pressure, and increase in cardiac output per minute. The average maximum increase in pulse rate was 39 beats per minute, usually occurring within 5 minutes after administration of the drug; some effect often persisted for more than 30 minutes.

A transient decrease of blood pressure occurred almost invariably about 3 minutes after the drug was given. This effect was seldom prolonged, and the initial decrease, though often marked, was never alarming. Since all subjects in the studies were required to remain in the recumbent position for an hour or more after any drug was administered, the orthostatic hypotension expected to result from tetra-

ethylammonium chloride could not be studied.

The cardiac output per minute increased in 10 of 11 subjects and in 9 of these the increase was striking. The change was mainly owing to increase in pulse rate, there being little change in stroke volume. The ballistocardiogram has generally proved to be an adequate instrument for measuring changes in cardiac output on the same patient at different times regardless of changes in rate<sup>23</sup>. However, Frisk and his co-workers<sup>10</sup> obtained results that differed from ours in 3 cases in which the cardiac output was estimated by the direct Fick. In one of these cases in which the complete data were given, the pulse rate before drug administration was 111. This brought up the question of whether or not the patient was in basal condition at the time the drug was administered.

The effect of this drug on digital cutaneous blood flow is considerable in high dosage (400 mg. or more) and under the conditions of the experiments; it is negligible in usual clinical dosage (300 mg. or less). In 4 of the 6 subjects who received the larger doses cutaneous flow in the fingers increased conspicuously. In 4 a moderate increase in blood flow in the toes resulted. In contrast to the effects of the larger doses, 4 of the 5 subjects who received the moderate dosage showed no increase in cutaneous flow in the fingers or in the toes. In the fifth, there were moderate increases in cutaneous flow in fingers and toes.

We do not imply that moderate doses of this drug have no clinical usefulness in peripheral vascular disease. Berry and associates<sup>2</sup>, Friedlich and associates<sup>9</sup>, and Coller and associates<sup>7</sup>, have shown the usefulness as well as the potency of these lower doses for the purpose of increasing the blood flow in certain skeletal muscles. Naide<sup>19</sup> has pointed out its



following this drug, was approximately the same as that in the control subjects, exposed to the same environmental temperature for the same length of time. We conclude that niacin, in these doses and under these conditions, had no measurable effect on digital cutaneous blood flow.

**Discussion.** The maximal digital blood flow constitutes a considerable proportion of the cardiac output and is primarily cutaneous<sup>18</sup>. It is enormous as compared with minimal digital blood flow. The former at 100 cc. per 100 cc. of tissue per min. represents a total flow (all fingers plus all toes)

In order to support such large increases in peripheral circulation either an increase in cardiac output per minute or a decrease in circulation elsewhere in the body must occur. As a matter of fact, we found that an increase in peripheral cutaneous blood flow was almost always supported by a cardiac output remaining at or increasing to at least a high normal figure. In the few instances when this was not the case it seems necessary to explain the support of the peripheral cutaneous increment in blood flow by vasoconstriction elsewhere (*i.e.*, "splanchnic" vasoconstriction). Fur-

TABLE II.—EFFECTS OF VASODILATOR DRUGS AND OTHER PROCEDURES ON THE DIGITAL CUTANEOUS CIRCULATION AND THE CIRCULATION ELSEWHERE ("SPLANCHNIC" CIRCULATION).

|                              | Meta-<br>bolism | Body Tem-<br>perature | Widespread<br>Effects |     |     | Local Effects<br>Blood Flow |      | "Splanchnic" |
|------------------------------|-----------------|-----------------------|-----------------------|-----|-----|-----------------------------|------|--------------|
|                              |                 |                       | BP                    | PR  | CO  | Fingers                     | Toes |              |
| Heat                         | +               | +                     | 0                     | +   | 0   | +++                         | ++   | --           |
| Food                         | ++              | +                     | 0                     | +   | +   | ++                          | 0    | 0            |
| Alcohol                      | +               | ---                   | 0                     | 0   | 0   | +++                         | +    | --           |
| Priscol                      | -               | -                     | +                     | ++  | 0   | ++                          | +    | -            |
| (small dose)<br>Methacholine |                 | 0                     | 0                     | ++  | ++  | 0                           | 0    | ++           |
| Tetraethyl-<br>ammonium      | 0               | --                    | -                     | +++ | +++ | ++                          | ++   | +++          |
| Niacin                       |                 | +                     | 0                     | 0   | 0   | -                           | 0    | 0            |

0 = insignificant change  
+ = slight but definite increase  
++ = considerable increase  
+++ = marked increase  
- = slight but definite decrease  
-- = considerable decrease  
- - = marked decrease

BP = Blood pressure  
PR = Pulse rate  
CO = Cardiac output per minute

of 400 cc. per min., the latter at some 100 cc. tissue per min. represents a total flow of some 8 cc. per min. An average cardiac output is approximately 3500 cc. per min. Increments in digital flow can amount, therefore, to some 10% of the total cardiac output per minute. Accompanying increases in cutaneous blood flow of the whole extremities are much greater, though not in proportion to the relative volumes of digits to whole extremities.

thermore, when striking increases in cardiac output per minute occurred, without proportional increases in cutaneous blood flow, it seems necessary to conclude that "splanchnic" vasodilatation prevented proportional increments in cutaneous blood flow.

Table 2 shows the effects of the various drugs and other procedures on the local circulations and shows their more widespread ("splanchnic," perhaps muscle) effects.

In the case of body heating, inges-



output per minute increased only slightly; blood pressure, pulse rate, and metabolic rate changed little; and there was a slight increase of body (mouth or rectal) temperature.

5. Food was an inconstant vasodilator. It increased the cardiac output per minute slightly but produced no significant change in blood pressure or pulse rate. Metabolic rate and body temperature were increased significantly. Food probably acted as a peripheral cutaneous vasodilator by raising body temperature.

6. Alcohol caused a considerable increase of digital cutaneous flow despite a striking decrease of body temperature. The cardiac output per minute, blood pressure, pulse, and metabolic rate, were insignificantly changed.

7. Priscol by vein in moderate doses caused an almost invariable, small, but definite increase of the blood flow through the digits. There was no significant change in the cardiac output per minute, although there was a slight increase of blood pressure. The pulse rate was insignificantly changed. There was a fall of body temperature.

8. Methacholine chloride caused no change in digital cutaneous flow in this set of experiments. Cardiac output per minute was increased. Blood pressure fell. Pulse rate increased, and body temperature remained unchanged.

9. Only with high doses (400 to 500 mg. intravenously) did tetraethylammonium chloride regularly produce significant increases in digital cutaneous blood flow. Other changes were produced by all doses (200 to 500 mg. intravenously), namely: an increase in cardiac output per minute, a fall in blood pressure, an increase in pulse rate, no significant change in metabolic rate, but a definite fall in blood

pressure, an increase in pulse rate, no significant change in metabolic rate, but a definite fall in mouth or rectal temperature.

10. Oral niacin caused no significant change in digital cutaneous flow, cardiac output per minute, blood pressure, pulse rate, or body temperature.

11. Heat, alcohol, moderate doses of Priscol, and food caused selective vasodilatation of the skin of fingers and toes in varying degrees. Methacholine chloride and tetraethylammonium chloride caused widespread vasodilatation, unselective for the skin of the fingers and toes.

12. High normal cardiac outputs usually accompanied digital cutaneous vasodilatation.

13. In general, cutaneous vasodilatation resulting from the drugs was not mediated by any increase in metabolism.

14. Drugs causing the greater increases in cutaneous blood flow caused the greater decreases in body temperature.

15. Sweating was an unimportant variable in decreasing body temperature, or in decreasing cutaneous blood flow, in the experiments on drugs or on food.

16. Mechanisms of action are discussed.

17. The vasodilator drugs which we studied are classified with reference to their actions on peripheral cutaneous blood flow and elsewhere as follows: a, those increasing only the cutaneous circulation; b, those increasing the cutaneous circulation and circulation elsewhere; c, those failing to increase the cutaneous circulation, with or without increasing circulations elsewhere.

We wish to extend our thanks to Ciba Pharmaceutical Products, Inc. for supplying us with Priscol (2-Benzyl 4, 5-imidazoline HCl). The name Priscol has recently been changed to Priscoline. We wish also to thank Parke, Davis and Company for the Etamon (tetraethylammonium chloride) used in the experiments reported in this paper. The work was supported in part by a grant from Smith, Kline and French Laboratories.





# PROGRESS OF MEDICAL SCIENCE

## GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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### HYSTERECTOMY

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To the laity "a very serious operation" in a female usually means hysterectomy. Despite the enormous advances which have been made in the technical side of pelvic surgery, many people still regard hysterectomy as an heroic procedure, as indeed it was regarded a bare 50 years ago. It is of interest to refer to a standard text book<sup>8</sup> of the "Gay Nineties" and to read "removal of the womb is occasionally demanded" and also that "the extra-peritoneal treatment of the pedicle is recommended" meaning that "the pedicle or cervix is brought outside of the wound and clamped there."

It took much courage for the early operators to suture the cervical stump and drop it back into the peritoneal cavity, at first with and later without drainage. The operative technique has steadily improved, and for many years the subtotal hysterectomy, leaving the cervix *in situ*, was the standard procedure. In the development of the operation, certain operators chose the vaginal route as the method of choice

while others preferred to extend the abdominal operation by removing the entire uterus. The pendulum has swung back and forth on the merits of each type of operation and in this review an attempt shall be made to present authoritative opinion supporting each view and let the readers get some idea of the relative values and also the risks involved.

In contrast to the rarity of hysterectomy 2 generations ago, it is at present probably the most frequently performed gynecological operation.

It is performed so often that many of the reparative and reconstructive pelvic operations are seldom seen in some clinics, as almost any deviation from the normal anatomy or physiology is deemed a sufficient indication for removal of the uterus, with or without the adnexa.

Miller<sup>16</sup> has questioned whether hysterectomy is a "therapeutic necessity or surgical racket" and in order to find the answer he made a study based on 246 hysterectomies performed

in 10 different hospitals, both large and small, in 10 different communities, in 3 midwestern states. He found a definite preference for the incomplete or subtotal excision over the total by more than 2 to 1. Since this study represents the work of many operators, this preponderance of the incomplete over the complete variety is interesting, if not entirely unexpected. In view of the enthusiasm and propaganda favoring the total operation, one might have expected a higher incidence for the complete extirpation. Apparently the general surgeon is not yet familiar with the frequently voiced desirability of the total operation, or else he is not impressed by the evidence so far presented. If the latter be the explanation, then it is readily understandable; for, taking everything into consideration, the total operation is more difficult than the subtotal, opinions to the contrary notwithstanding. Furthermore, except for the obvious fact that future disease of the cervix is eliminated, the other advantages sometimes claimed for complete hysterectomy still remain to be proved. When hysterectomy is necessary, he prefers the total operation for the specific and obvious advantage mentioned above. However, he is quite unimpressed by the evidence presuming to prove a lower mortality and morbidity for the total operation. Until thoroughly comparable cases treated by both methods have been evaluated, the benefits of total over the subtotal hysterectomy will remain a much discussed question with a single positive advantage—elimination of the cervix—in favor of the total procedure. While this advantage seems real and sufficient enough to many of us, Miller questions whether it justifies the potential added risk to the patient entailed by forcing total hysterectomy upon the occasional operator.

Of the symptoms leading to medical

care, bleeding heads the list. Other complaints include abdominal pain (9.7%), pelvic pain (7.7%), and backache (5.2%). Almost 10% (9.3%) sought medical care for secondary symptoms. Under this heading are included fatigue, irritability, nervousness and headache, complaints commonly listed as functional in character. It is interesting that 17.4% had no complaints, as most patients subjected to major surgery usually have a reason for seeking medical care. As bleeding was the prominent symptom, it is not surprising to discover that uterine fibroids dominate the list of palpable diseases. However, many clinically suspected fibroids were later found to be either nonexistent or else extremely small. The significant observation in this cataloguing of palpable findings is the fact that 18.6%, almost 1/5 of all the women operated upon, were recorded as having no disease of the pelvic organs. This absence of palpable disease may, in part, be explained on the basis that the patient may have had troublesome symptoms, such as bleeding, without gross disease of the generative organs. Even so, this figure seems high. It is startling to note that 76 (30.8%) showed no histopathology of the organs removed. This figure is especially revealing, since included as acceptable pathologic indications are disease of the adnexa, prolapse, hyperplasia of the endometrium, and relaxation. In other words, almost 1/3 of the patients in this series revealed no histologic evidence of disease. This astonishing figure warrants scrutiny. The facts that 17.4% presented no symptoms, and 18.6% had no palpable pelvic disease, do not of themselves permit the assumption that approximately  $\frac{1}{3}$  of the patients in this series had acute remunerative or hip-pocket hysterectomies. Some patients requiring operation may have been unaware of the fact that they harbored a pelvic

neoplasm, such as an ovarian or uterine tumor. Yet it was deemed feasible to remove such an asymptomatic neoplasm.

As subtotal hysterectomy had been the standard procedure for many years when the abdominal approach was selected, it is understandable that most of the current literature is concerned with the total operation since the effort is being made to have it replace the older operation and some very convincing reports have been presented.

Danforth<sup>5</sup>, reporting a series of 500 cases of total hysterectomy, states that cervixes which are not entirely normal are often troublesome after a subtotal operation. Discharge which does not yield well to treatment is often met with. The poorly nourished stump has a diminished resistance and does not respond as well to the usual forms of treatment as when the entire uterus is present. Bleeding is sometimes seen. The removal of the stump is sometimes indicated. For both of these reasons the elimination of the cervix seems desirable provided it may be accomplished without increase in the mortality rate, or, in any event, an increase not greater than the number of cases of stump cancer would account for. Fortunately, in well staffed clinics, this is entirely possible. Danforth is not in agreement with an opinion recently expressed that the total operation should be recommended for all operators. In the series there were 2 deaths, a mortality rate of 0.4%. Without a thorough familiarity with pelvic anatomy and technique, there is a very definitely greater danger in the total operation. Among these particularly are injury to the urinary tract and hemorrhage.

A rise of temperature to 100.4 F. on any 2 days, excluding the first 24 hours, brings the case into the morbid list. According to this standard, 141

patients (28.2%), had a morbid recovery. In 2 cases ureteral injury occurred, in 1 case the ureter being tied while in the other it was cut. Both patients recovered, although nephrectomy was needed in both cases. The bladder was opened 4 times. Immediate suture was done and a permanent catheter put in. All of these recovered without trouble.

Although the subtotal operation was formerly the routine procedure at the University of Iowa, Mengert and Stoltz<sup>15</sup> state that conditions are now reversed but they do not advocate the general adoption of elective total hysterectomy. In their series of 1925 operations, a complete operation was essential in the 12% of the operations that were performed for malignant disease. If it be granted that removal of the cervix is desirable in the presence of pelvic inflammatory disease, then total hysterectomy was desirable in an additional 329 patients. In other words, removal of the cervix was essential or desirable in 563 patients, or 2 in 7. Any university department of obstetrics and gynecology actively engaged in training young men must, therefore, face the necessity of teaching the techniques of total hysterectomy. The majority of the operations (63.4%) were done by assistant residents or residents. The principal indications for hysterectomy included fibromyoma, functional bleeding, pelvic inflammatory disease, benign and malignant ovarian and malignant uterine tumors. Ureters were injured in 10 women, with 9 repairs, at the time of initial operation. Subsequent operation for reimplantation was necessary in one patient. Morbidity rates were similar to those of any hysterectomy series, irrespective of the type of operation. Death occurred in 38, or 1.97% of the patients. Twenty-nine (3.01%) of the fatalities occurred in the first chronological half of the series and 9 (.094%)

in the second. Infection of some type, chiefly peritonitis, accounted for 22 of the 38 deaths.

In the experience of Munnell<sup>18</sup> at Bellevue Hospital in New York, the mortality rate for total hysterectomy is higher than for subtotal hysterectomy in a series of 215 total hysterectomies. Increased skill from doing more and more total hysterectomies as well as proper selection of cases should reduce the mortality from total hysterectomy. Proper selection of cases involves the ease with which the operation may be performed, the skill of the operator, the patient's general condition, the degree of fixation of the uterus, adhesions, obesity, and so on. Increased mortality is the only valid objection to the procedure and even this is not a tenable argument when the number of deaths from the possibility of cancer developing in the residual cervical stump are taken into account. The prevention of cancer of the cervical stump is an adequate reason for performing total hysterectomy in benign cases as long as the operation does not introduce an element of extra danger to the patient. In so far as postoperative reaction is concerned, patients having had total hysterectomies will run a slightly higher temperature for a longer period of time. Catheterization is slightly less frequent in total hysterectomies than in subtotals. Postoperative distention is approximately the same in each group. The only postoperative complication that can be considered a valid objection is the possibility of injury to the bladder and, or, ureters; proper technique should avoid this complication as well as that of prolapse or shortening of the vaginal vault. Sexual response in women following hysterectomy is not significantly different with the cervical stump remaining than with the cervix removed. Indeed, the cervix, uterus, and ovaries seem to

have little to do with libido or sexual satisfaction. Where there are changes in libido or sexual satisfaction following hysterectomy, the cause of these changes is undoubtedly psychogenic.

The reasons which Hunt<sup>10</sup> gives for being dissatisfied with the subtotal operation are the distressing symptoms of leucorrhea, occasional bleeding from the cervical stump or polypoid protrusion. He reports the complete removal of the uterus in 243 cases, without a mortality, without an injury to the bladder or ureters and with no added hospitalization period. Bleeding during the operation was not a problem. Postoperative recovery did not indicate pelvic infection. This was less in the total than in the subtotal operation. Cutting across the cervix opens a field for infection, even though the canal has been thoroughly cauterized. Cauterized tissue becomes necrotic and a fertile field for infection, which is conducive to thrombophlebitis. There has been only 1 case that presented any postoperative bleeding and this was easily controlled. Such occurrence is negligence and due to failure to close adequately the vaginal vault; in this instance, at the side of the vaginal vault suture. At this angle vaginal mucosa may retract and not be included in the suture and subsequently bleed. The average postoperative stay in the hospital was 14.7 days. The time of operation was not prolonged appreciably over that of subtotal hysterectomy. The average time taken for operation was less than 1 hour. Frequent inquiries as to marital relations following this procedure have resulted in satisfactory replies in most instances. There has been no distressing leucorrhea, no periodic bleeding and naturally no carcinoma following the procedure. He believes total hysterectomy is preferable in the vast majority of cases to subtotal hysterectomy for lesions re-

quiring the removal of the uterus but does not by any means advocate the complete removal as a routine. Each case has to be individualized and the appropriate procedure decided upon. The age of the patient, the condition of the cervix, the anatomical obstacles at the time of exploration and to some extent the wishes of the patient are to be considered. If the patient is fat, the pelvis deep and inaccessible, the lower uterine segment fixed by fibrosis, or endometriosis with a firmly adherent rectum and rectosigmoid, total hysterectomy is contraindicated. A normal cervix in the nullipara does not necessitate the removal of the cervix. It is likewise preferable not to do so in a young individual without cervical disease or familial cancer tendencies. However, when the individual is in the mid-period of life, near or after menopause, has borne children, has an infected cervix, enlarged, eroded or scarred by lacerations, with or without appreciable leucorrhea, he believes the cervix should be removed along with the fundus. It is to be admitted that the incidence of cancer of the cervical stump is not great and may not be considered as an indication for total hysterectomy. Certainly not, if the mortality of the operation exceeds the incidence of cervical stump cancer.

The increasing safety of the operation is shown in the paper of Siddall and Mack<sup>21</sup> who review 6692 abdominal hysterectomies performed at Harper Hospital from 1928 to 1945, inclusive, revealing a marked decline in mortality. In an effort to determine the factors responsible for this improvement, a comparison was made of the results during the first and the last 5 year periods of the series. This study showed that along with an increase in the numbers of hysterectomies of all types there was also a steady growth in the proportion of total hysterec-

tomies. The mortality curve for the 18 year span demonstrated a consistent lowering of the death rate for hysterectomy from 3.7% in the first 5 year group to 0.78 in 1941-1945. Subtotal hysterectomy mortality declined from 2.8 to 0.76%, while panhysterectomy deaths dropped from 7.3% to 0.80.

In an investigation of the principal causes of death it was found that while infection, hemorrhage (shock and heart failure), and embolism played the main roles, their incidence in the last 5 year group was greatly-reduced over that of the first period. The part played in this reduction by various factors such as better selection of cases, blood transfusion, and chemotherapy was considered. It seemed evident that the greatest responsibility in the lowering of hysterectomy mortality was ascribable to the increasing use of blood transfusion. This factor antedated the advent of chemotherapy, which probably also caused some improvement though not statistically shown in this series. Certainly, the tremendous improvement in results now permits a very welcome extension in the use of the complete operation. Nevertheless, there are several reasons to believe that the mortality figures of the 2 operations are not altogether comparable and consequently do not give the true picture regarding the relative operative dangers. This is evident from the fact that, in accord with prudent surgical judgment, the poorer risk patients tend to have the less formidable operation, except in the rather few instances where panhysterectomy is absolutely imperative. The views formulated at the Mayo Clinic are always of importance because of the enormous clinical material of that group. As a result of his experience in that clinic, Masson<sup>1,3</sup> is satisfied that when total abdominal hysterectomy is done by competent

surgeons in a large series of cases, the end-results are better, the morbidity is less, and the mortality no greater than when subtotal hysterectomy is done in a similar series of cases by the same experienced surgeons. The occasional operator or any surgeon who has not taken special pains to become thoroughly familiar with the technique of a total abdominal hysterectomy is advised to continue doing the subtotal operation in a large majority of his cases even at the risk of leaving an infected cervix which might require treatment or removal at a later date.

Danger of cancer developing in the cervical stump is not the only reason for its removal, but cancer developing at this site is more frequently reported than formerly. Statistics are very unreliable in such cases. The weight of statistical evidence, however, is that cancer occurs in probably not more than 1 or 2% of cases in which a subtotal hysterectomy has been performed for benign conditions.

From January 1, 1934, to December 31, 1938, inclusive, hysterectomy was performed for benign conditions in 3149 cases at the Mayo Clinic. Among the 1776 cases in which total abdominal hysterectomy was performed, 22 (1.2%) of the patients died; among the 766 cases in which subtotal abdominal hysterectomy was performed, 7 (0.9%) of the patients died, and among the 607 cases in which vaginal hysterectomy was performed, 9 (1.5%) of the patients died. During the years 1936, 1937 and 1938, Masson performed 784 hysterectomies with 6 deaths, a mortality of 0.76%; 196 of these were vaginal hysterectomies with 1 death, a mortality of 0.51%. In recent years he has become more and more convinced that a total hysterectomy is advisable in most cases in which it is necessary to remove any of the uterine body of women who have been

delivered of children by the vagina and who are close to or at the menopausal age, provided the surgeon is familiar with the technique of such an operation and can complete it within an hour. The 3 most important considerations in a low operative mortality are: 1, a well given anesthetic; 2, adequate exposure; and 3, no unnecessary delay in completing an operation.

A few years later, another report from the same clinic was presented by McKinnon and Counseller<sup>14</sup> which analyzed 2684 hysterectomies of which 1920 were total with a mortality of 0.78% and 764 were subtotal with a mortality of 1.04%. These mortality figures are excellent and show a lower mortality for the total operation as against Masson's figures which showed a higher mortality for the total operation. Nevertheless, these authors still perform the subtotal operation in certain cases. They state that total hysterectomy is favored by the following consideration: 1, The cervix as a possible source of subsequent malignant change is eliminated. 2, The cervix as a focus of infection is removed completely. 3, A more stable vaginal vault is obtained and secondary operations are obviated. 4, The incidence of postoperative pulmonary emboli and postoperative thrombophlebitis is lower. 5, The mortality rate is lower.

Subtotal hysterectomy also is favored by various considerations: 1, The postoperative reaction of the patient is less marked. 2, The incidence of urinary complication is lower. 3, There is not any danger of secondary hemorrhage from the vaginal vault. 4, In cases in which infection is present at the time of surgical intervention the mortality rate is lower.

Thus far the more radical view in regard to hysterectomy has been presented. Now let us see what some

of the more conservative gynecologists think about the subject. Martzloff<sup>12</sup> states that in view of the fact that cancer may develop in the residual cervix after supravaginal hysterectomy for benign uterine disease, it has been proposed by some observers that performance of total hysterectomy as an inflexible routine would eliminate this complication. These observers also state that in competent hands the mortality from total hysterectomy is little if any more than that following subtotal hysterectomy and they advocate, therefore, without reservation, the total operation when hysterectomy is to be done.

On the other hand there are numerous opponents to the proposal that total hysterectomy be performed in every instance in which hysterectomy is to be done. This does not mean that panhysterectomy should never be employed for benign disease but that its use should be a matter of individualization and restricted to those instances in which there is an obviously pathological cervix and the operation can be done without undue hazard. The basis for objection to total hysterectomy as a routine is that rigid adherence to the procedure leads to an increased operative mortality and morbidity; the operation is ordinarily inadequate to cure patients who have an established but unsuspected cervical cancer, and the hazard of subsequent cancer-change in a previously noncancerous cervix is not as great as the increased mortality inherent in the total operation. Finally, the objection has been raised that the total operation is no guarantee that cancer may not develop later in the vaginal vault.

The relative mortality of these 2 operative procedures is difficult to compare. It is obvious that when exposure is difficult or the patient is or has become a poor surgical risk because of hemorrhage or some other acute

contingency, the supravaginal operation is the only procedure possible or permissible. However, some of the zealous advocates of routine total hysterectomy deny that it possesses any appreciably increased hazard and apparently do not recognize the existence of situations in which the procedure is well nigh impossible. The overwhelming weight of competent gynecological opinion is of the opposite view and considers the total operation as one of election to be done only when the indication exists and the operation does not involve undue hazard or frank foolhardiness.

The value of total hysterectomy for cancer prophylaxis is granted. However, as Martzloff views the situation, the important consideration in deciding to do an abdominal panhysterectomy is not the presence of a myomatous uterus, or the obvious desirability of removing simultaneously a symptom producing cervix, but the ability to do the operation without additional risk to the patient. The presence of benign disease of the cervix and the fear of subsequent cancerous change is, he believes, no special indication for panhysterectomy if this procedure entails an increased operative hazard. The so called "angry, red appearance" of a bleeding circumostial vermilion zone offers real fuel to the suspicion that the fire of cancer is near at hand. The statement is therefore frequently encountered that an "eroded" inflamed cervix offers special danger of subsequent development of cancer. There is, however, little if any factual information to support this constantly repeated assumption. All of the truly early *bona fide* cancers he has seen so far have occurred on relatively normal appearing cervixes. It is extremely doubtful that one can foretell from the appearance of a cervix involved in a benign inflammatory process whether it is more likely to de-



velop cancer than a normal appearing cervix. Nulliparity is no guarantee against subsequent cancer development. Therefore, the admonition that when hysterectomy is indicated for benign uterine disease, a diseased cervix is a strict indication for panhysterectomy, because it is particularly prone to develop cancer if left *in situ*, becomes largely a matter of individual opinion, unsupported, as far as he can ascertain at this time, by acceptable proof. The incidence of cancer in the residual cervix after supravaginal hysterectomy is less than 1%. Total hysterectomy, except when used as an elective procedure by well qualified individuals has a mortality rate definitely in excess of the supravaginal operation. The difference in mortality between the 2 operative procedures is evidently in excess of the incidence of *bona fide* cancer which may develop in the residual cervix after supravaginal hysterectomy. There is good reason, therefore, to doubt the wisdom or factual basis for advocating panhysterectomy as a fixed routine when hysterectomy is to be done for benign uterine disease in order to avoid the possibility of subsequent cervical cancer.

Cashman and Frank<sup>3</sup> admit that the advocates of total hysterectomy are correct in maintaining that a subtotal hysterectomy which leaves an infected cervix, or one that becomes infected subsequently, is an incomplete operation. But many of these surgeons do total hysterectomy in selected difficult and subtotal hysterectomy in handicapped patients and in technically difficult cases, with the result that in the latter group no treatment of the cervix is carried out, and the patient is left with an infected cervical stump. Their mortality for subtotal hysterectomy has been below 1% in consecutive, unselected cases and the cervix has been adequately cared for by deep

cauterization in all but 3 cases. There has been no necessity for subsequent treatment of the cervical stump for inflammation or neoplasm. As long as that situation prevails, they see no reason for changing to total hysterectomy. They have grave doubts as to whether they could keep the mortality rate at that level if they applied total hysterectomy routinely to a similar series which includes all of the physically handicapped, the adipose, the inflammatory, and the technically difficult cases.

Infection plays an important role in the mortality of hysterectomy, total or subtotal. Infection is a factor in the occurrence of phlebitis, embolism. If infection could be much reduced or eliminated, the mortality and morbidity of hysterectomy would fall markedly. For many years Cashman and Frank have thought that the cervix is the principal source of postoperative infection after hysterectomy and have advocated deep cauterization as the best method of sterilizing the cervix preliminary to hysterectomy. The purpose of this procedure is to destroy completely the infected cervical mucosa and glands. The extent and depth of the cauterization depends on the extent of the erosion and cystic condition in the cervix. Each radial cut with the cautery blades varies from  $\frac{1}{8}$  to  $\frac{1}{4}$  inch in depth. One should aim to cauterize too deeply rather than too superficially. In the subsequent care of the patient, stricture can be disregarded, for when hysterectomy and cauterization are combined, the cervix can be permitted to heal with obliteration of the canal. The serious results of cauterization of the cervix, such as cellulitis and peritonitis, for example, which are stressed by some authors, are due in most instances, Cashman and Frank believe, to incomplete cauterization which leaves a zone of infected glands beneath the cauterized tissue.

Deep cauterization is preferred because sections of the cervix show that the inflammatory process is frequently deep seated and that it is necessary to cauterize deeply in order to eliminate it.

Formerly, they cauterized only the cervixes that did not seem to be normal. However, some cervixes, which looked normal at the time of subtotal hysterectomy, were found to be markedly inflamed on later examination. This is probably the result of circulatory changes in a glandular structure which predispose to infection. Preliminary to subtotal hysterectomy, they cauterize practically every cervix whether it appears normal or not. In some clinics the cervix is cauterized and permitted to heal before subtotal hysterectomy is done. This is done to eliminate the danger of peritonitis following cauterization of the cervix and immediate hysterectomy. In their experience, this danger has been greatly exaggerated. In fact, they feel that there is no method other than cauterization at the time of operation that so certainly sterilizes the cervical canal. The cauterized cervix opens into the vaginal canal and the microorganisms that appear later in the slough are saprophytes, and there is less danger of peritonitis than if the infected cervix with its pyogenic organisms is left in place.

In a study of 87 cases of cervical stump bleeding observed at Johns Hopkins Hospital by Davis and Cheek<sup>7</sup> there were 40 cases (46%) which revealed a cancer of the cervix. Of these 40 there were 6 (15%) in whom the cervix appeared benign. They believe that the only sure way to detect early carcinoma after a subtotal hysterectomy is to view any bleeding with alarm, regardless of the appearance of the cervix.

Regardless of a history suggesting the presence of menstruating endome-

trium, regardless of the appearance of the cervix and regardless of estrogen therapy, every patient who has vaginal bleeding at any time after a subtotal hysterectomy deserves a biopsy of the cervix and a gentle curettage of the cervical canal. It is hoped that pre-operative study will decrease the number of patients on whom a subtotal hysterectomy is performed in the presence of an unrecognized early carcinoma of the cervix.

**VAGINAL HYSTERECTOMY.** Many gynecologists are partial to removal of the uterus by the vaginal route; in fact, some men are such extremists as to consider this route desirable in almost all cases. It is important not to be carried away by the enthusiasm of such men but rather to seek the experience of those who practice this operation with a balanced judgment. According to Danforth<sup>6</sup> one of the greatest advantages of the vaginal removal is that the cervix is done away with. The danger of cancer in the retained stump is not a great one, although its existence must be acknowledged, but the stump may be troublesome as a source of leucorrhea, bleeding, and as a focus of infection. In a series of 1510 hysterectomies of all types in his clinic the vaginal operation was carried out in 32.3%. He does not believe that vaginal hysterectomy should be done in all cases, or in too great a proportion of the total number of patients operated upon, but he is convinced that the operation has a very definite value. The indications for which these operations were done were leiomyoma, prolapse, menorrhagia, retrodisplacement, outlet relaxation of greater or less degree, and endocervicitis or injury of the cervix.

Larger myomas may be removed vaginally by excising the uterus piecemeal, or by morcellation. This is a procedure which demands a considerable degree of familiarity with the technique

of the operation and which occupies a limited field.

Approach from below is contraindicated by a number of conditions. When hysterectomy is indicated in the presence of extensive residues of pelvic inflammatory disease the excision is best performed abdominally. The adhesions which may be found in these cases render the vaginal operation difficult and hazardous. Previous pelvic operations may be followed by adhesions sufficiently extensive to render vaginal work difficult. Danforth has, in a number of instances, removed the uterus from below after some procedure for the shortening of the round ligaments had been done abdominally, but the operation has usually been difficult. It should not be attempted unless the operator has had a considerable experience with vaginal surgery. Cases in which endometriosis is suspected are better approached from above as the dense adhesions characteristic of this condition are hard to manage from below. Ovarian cysts, if not adherent, may be punctured and removed from below with no great difficulty, but the impossibility of being certain as to the exact character of the cyst before the abdomen is entered makes it wiser to treat them by abdominal incision.

Danforth does not recommend the operation for the treatment of carcinoma of the uterine corpus. A very important early step in the performance of hysterectomy for corpus cancer is the blocking of the broad ligaments by placing straight 8 inch clamps alongside the uterus on either side to prevent the pushing out of cancer cells through the lymphatic vessels of the broad ligaments. This may be done immediately when the approach is made from above. When the operation is carried out from below, the upper part of the broad ligaments is not occluded until late in the operation, while in the

earlier stages the uterus will have been subjected to a considerable amount of handling. In most of the cases of corpus carcinoma, it is technically possible to remove the uterus from below, but the impossibility of early closure of the broad ligaments interposes a serious objection to the employment of the operation.

In Danforth's series of 517 vaginal hysterectomies, there has been no death. Although mortality has been absent, morbidity has not. It is not possible to do hysterectomy by any method without some morbidity, as a bacteria laden area is invaded whatever the type of operation chosen. The morbidity is somewhat higher in the vaginal operation than in either the total or the subtotal abdominal hysterectomy. By the standard of the American College of Surgeons, that is, a temperature of  $100.4^{\circ}$  on any 2 days excluding the first, 42.1% of the cases must be placed in the morbid group. In spite of this fact, convalescence has been, as a rule, smooth. The hospital stay, in uncomplicated cases, is 11 or 12 days. Drainage is not used except in the cases of prolapse in which the dissection is rather wider than when the operation is done for other reasons. In cases in which the uterus protrudes from the introitus, and the broad ligaments are interposed between the bladder and anterior vaginal wall with the freed pubocervical fascia as an additional support, a small drain or rubber tissue is placed in the wound at the vaginal vault and is removed in 24 hours.

There were some more serious sequelae. Postoperative bleeding occurred in 15 cases. In all the cases in which bleeding occurred during recovery, it was easily controlled by a clamp or suture at the vaginal vault. In no case did a notable loss of blood occur. Pelvic abscess required opening in 7 cases. A vesical injury occurred in 3 cases.

The Department of Gynecology in the Presbyterian Hospital in Chicago has been a staunch advocate of vaginal hysterectomy for many years and the results obtained in that clinic justify the enthusiasm, since Campbell<sup>2</sup> reports 2798 operations with 6 deaths or a mortality of 0.214%. Therefore, he believes that vaginal hysterectomy should be chosen whenever feasible because it permits a more regular correction of all defects than do other procedures and causes less discomfort to the patient. No abdominal scar is produced and pulmonary complications and emboli are less frequent while thrombophlebitis and pelvic abscess are less common. Trauma to the bowel, postoperative adhesions, ileus and bowel obstruction are infrequent and gas pains are less severe. He believes it is less radical and safer than irradiation and affords a safe approach to many forms of adnexal pathology. Peritonealization can be accomplished as accurately as by the abdominal route. Stump carcinoma and persistent cervical discharge are prevented. He agrees with many who have advocated vaginal hysterectomy rather than abdominal hysterectomy in poor operative risks. It then seems logical that vaginal hysterectomy is an even safer procedure in patients who are in better operative condition. Previous abdominal surgery need not always contraindicate vaginal removal of the uterus. The technical skill of the operator is of no greater importance than is the choice of method of approach or preoperative preparation of the patient, such as: eradication of foci of infection, correction of anemia, vitamin, protein and fluid balance and restoration of the normal vaginal flora. Meticulous hemostasis is vitally important.

In order to get the viewpoint of one who is a real enthusiast about vaginal hysterectomy, we present the indications for the operation as given by

Blain<sup>1</sup>: 1, *Benign neoplasm of the uterus*. These tumors may be large and multiple, those extending above the umbilicus having been removed vaginally following morcellation. 2, *Procidencia uteri*. Vaginal hysterectomy was possibly first performed for complete descensus. Many of the present day writers, unacquainted with this field of surgery, consider prolapse the only indication for this procedure. 3, *Extensive laceration, erosion, ectropion, and leucoplakia of the cervix*. This type of lesion is frequently precancerous and should be eradicated when a hysterectomy is performed. 4, *Functional bleeding*, especially in the menopausal period, which does not respond to endocrine therapy. 5, *Chronic subinvolution of the uterus*. 6, *Uterine polyps*, especially those showing a tendency to recurrence or exhibiting early malignant changes. 7, *Persistent uterine leucorrhea*. 8, *Stenosis of the cervix* which has not responded to less radical treatment, such as that following radium therapy producing pyo-uterus. 9, *Chronic metritis*. 10, Vaginal hysterectomy constitutes the most effective treatment for *carcinoma of the corpus uteri*. The uterus should be removed intact. Radium and Roentgen-ray therapy, while replacing surgery in carcinoma of the cervix, should be used only as an adjunct to surgery in carcinoma of the fundus. The use of radiation in younger women without proved malignant disease is less scientific and more radical than vaginal hysterectomy because of the destructive action of the rays on the ovaries. In Blain's opinion, there is no definite contraindication, although there are certainly instances in which the transabdominal approach is preferable, and the decision as to method must be based upon the wisdom of the surgeon. There is no objection, should the vaginal approach be found impractical, to complete the operation by the abdominal route.

Opposed to such enthusiasm is the opinion of Cogswell<sup>4</sup> who compared the results and postoperative courses of a series of abdominal hysterectomies with one in which the operation was done by the vaginal route. He states that if a vaginal hysterectomy could be done with ease in an obese individual, it would certainly be preferred to an abdominal operation. Surgery through a fat abdominal wall with a thick, bulky omentum always makes any operative procedure more difficult and is attended by a greater danger of postoperative hernia, but it is often impossible to determine the presence of masses or fixation of the pelvic viscera when examining a fat individual. The morbidity in the obese was higher in the vaginal series than in the abdominal. There was no death in either group. The perils encountered in a difficult laparotomy on an obese individual cannot compare with those present in a poorly selected vaginal hysterectomy. If it can be definitely determined before the operation that there are no abdominal tumors and that the uterus and adnexa are not fixed so that the uterus can be prolapsed with some traction, the indications for a vaginal hysterectomy may be present. He concludes that prolapse of the uterus is the only indication for a vaginal hysterectomy. The morbidity is higher in vaginal hysterectomy than in abdominal hysterectomy, except in procidentia. The smoother convalescence of older patients upon whom a vaginal hysterectomy was performed is explained by the fact that all the patients in this group were operated upon for procidentia. Excluding cases of procidentia, the postoperative complications are complaints are more numerous in the vaginal group than in the abdominal group.

**INJURIES TO THE URINARY SYSTEM.** With the increase in the number of total hysterectomies that are being per-

formed, it would seem that there has been an increase in number of injuries to the urinary system, judging by the many papers which have been written on the management of such injuries. In the Woman's Hospital in New York, according to Murphy<sup>19</sup>, injuries to the ureters and bladder were 10 times more frequent after total than after subtotal operation. The most serious of these injuries were the 4 ureterovaginal fistulas. They resulted in 1 death, 1 nephrectomy, the function of 1 kidney destroyed by radiotherapy and 1 patient who, although she could not be traced, would probably require nephrectomy in order to be cured. The seriousness of unrecognized ureteral injury with late renal complications cannot be minimized. All of these patients were operated upon by well-trained surgeons in an outstanding hospital. Under these conditions and from the urologic viewpoint, the greater frequency of ureteral and bladder injury following complete hysterectomy, should make one hesitate before adopting this operation as a routine. One may conclude therefore that routine complete hysterectomy is not advisable because of the greater frequency of urinary infections and ureteral and bladder injuries. In a further discussion of this subject<sup>20</sup> Murphy states that trauma to the ureter may or may not be observed during operation. If the operator is cognizant of the injury, he should repair it immediately. A very small injury to the wall of the ureter should be sutured, the peritoneum closed over the injured area and an extraperitoneal drain inserted. If the injury to the wall of the ureter is extensive, or if it is completely divided, an end-to-end anastomosis should be carried out. An indwelling ureteral catheter should be inserted into the ureter to prevent edematous obstruction of the ureter at the site of the anastomosis and to provide good urinary drain-

age during the healing of the ureter. If a large section of the ureter has been removed an anastomosis is impossible. In this instance, the lower end of the ureter should be ligated and the upper end reimplanted into the bladder. This operation is not difficult or time consuming and gives excellent results. Only rarely will so much of the ureter be removed that it will not reach the bladder. When this happens the ureter may be simply ligated or it may be implanted in the bowel. If the injury to the ureter takes place during a very difficult operation, when the patient's condition will not permit any of these procedures, both ends of the ureter should be ligated, with death of the corresponding kidney. This should not often be necessary if one is familiar with the various methods of treating ureteral injuries. When the ureteral injury is not observed during operation, a uretero-abdominal, or more frequently a uretero-vaginal, fistula results. Occasionally it may cause peritonitis, and in his opinion unrecognized ureteral injury accounts for some of the deaths from peritonitis that follow hysterectomy. In other cases, a pelvic abscess or an extraperitoneal abscess along the course of the ureter or kidney from extravasation of urine may be seen as a consequence of ureteral injury. If peritonitis follows hysterectomy and if there are signs of free fluid in the abdominal cavity soon after operation, the possibility of unrecognized ureteral injury should be considered. The diagnosis of ureteral injury should be made by cystoscopic study and as soon as the diagnosis is definitely established, nephrostomy is indicated to divert the urine from the injured ureter. This may be a life saving procedure. If there is no improvement following this operation, it may be necessary to drain the abdominal cavity. As soon as an abscess is formed extensive drainage should be provided and nephrostomy

may also be necessary. The outcome of unrecognized ureteral injury may be the formation of a uretero-abdominal fistula. In this event an attempt to pass a ureteral catheter by the injured area in the ureter should be made, for if this maneuver is successful, the fistula may be closed as happened in one of his cases. This will not be possible in the majority of cases. Before attempting another laparotomy to close the fistula, about 6 weeks should pass and, if the operation is then necessary, the ureter should be divided and reimplanted into the bladder. Ureterovaginal fistula is the most common complication caused by unrecognized ureteral injury. In this complication an attempt should be made to pass an indwelling ureteral catheter by the injured area in the ureter to aid in the closure of the fistula. Some of these fistulas will close spontaneously so that the operation is not indicated until 6 or 8 weeks have passed. The ideal operation for the cure of ureterovaginal fistula is reimplantation of the ureter into the bladder. If another laparotomy is contraindicated, nephrectomy will occasionally be necessary. Fortunately, ligation of both ureters is rare following hysterectomy. It is more apt to result from total than from subtotal hysterectomy. This is a serious complication and carries a mortality of 33%. Subsequent to hysterectomy, the urinary output must be carefully tabulated so that the diagnosis of this grave complication can be suspected as soon after operation as possible. In a suspected case cystoscopy, to corroborate the diagnosis, is urgent and immediate treatment should be instituted to provide urinary drainage and forestall advancing uremia. How should bilateral ureteral ligation be treated? Should the abdomen be reopened and the ureters de-ligated or should nephrostomy be performed? Before this question can be decided one must careful-

ly weigh all the facts involved in each individual case.

Abdominal de-ligation may be chosen if the original operation was not prolonged or unduly difficult and if the patient is young and in good condition when the diagnosis is made. In an older person who has already withstood a difficult operation and whose general condition is not good when the diagnosis is made, nephrostomy should be the operation of choice. It is Murphy's opinion that in the majority of cases the indications for nephrostomy will overbalance those for abdominal de-ligation. Bilateral ureteral ligation usually happens during a difficult operation, so that the majority of patients will be in a precarious condition when the diagnosis is made. Some patients will be middle-aged or elderly women who have been operated on for carcinoma of the fundus. Many of them will be in the midst of a stormy post-operative period with a high temperature and an already over-burdened circulatory system. To reopen the abdomen in such cases would carry a very high mortality. It has been their experience at the Women's Hospital that reopening the abdomen for any cause within 48 or 72 hours involves a high mortality from shock and sepsis.

In the experience of the urologist, Moore<sup>17</sup> states that accidental injury of the ureter during the course of pelvic operation is not uncommon. This type of serious accident has a mortality rate of 33.3% for bilateral ureteral injuries and 18.8% for the unilateral injuries. The incidence of ureteral ligation as a complication of all operations on the female genital organs may be placed at between 1 and 3%. Many cases are not reported and many may not be recognized. The proportion of unilateral to bilateral injury is 6 to 1. Injury of the ureter may occur at the hands of the most skilled surgeon. Urologists believe that such injuries

are preventable. They have advocated the preoperative insertion of inlying ureteral catheters when difficult pelvic surgery is anticipated. Those indwelling catheters can serve as a guide so that the ureter can be more easily recognized and avoided. However, many gynecologists are loath to accept this precautionary measure. They contend that the catheters give a false sense of security and alter the normal position of the ureters, making the ureter more liable to injury. In many instances the catheters cannot be located by palpation and can give rise to infection, ureteral colic, and oliguria. There is an abundance of evidence indicating that in spite of these objections the preliminary insertion of ureteral catheters is a wise precautionary measure. The simple ligation of one ureter seldom is recognized at the time of operation. If the accident is discovered during the operation, immediate de-ligation followed by the insertion of a ureteral catheter would be adequate treatment. Crushing by a clamp requires essentially the same treatment as a severed ureter because of the probability of subsequent sloughing or dense cicatricial contracture. There are several procedures that may be adopted to repair this type of accident. End-in-end anastomosis has proved more satisfactory than end-to-end anastomosis of the injured ureter. A small opening above the anastomosis through which the ureteral catheter is passed to the renal pelvis and brought out of the flank for temporary diversion of the urinary stream has been advocated following the repair of this type of injury. The author warns that although the immediate results of this type of repair may be good, the patient may require frequent and systematic dilations of the ureter; otherwise, slow hydronephrotic atrophy may necessitate late nephrectomy. If the ureter is injured low in the pel-

vis, an attempt can be made to anastomose the ureter to the bladder. Cutaneous ureterostomy is mentioned only for condemnation, although this procedure may be regarded at the time as a conservative procedure. Although uretero-intestinal anastomosis may seem a good procedure, few patients are prepared for this type of surgery as the risk would be greater than in a planned operation of this type. Ligation may be the operation of choice, especially after a difficult and long operation and if the patient's condition is considered to be poor. Before ligation of the proximal stump of the ureter, it is wise to palpate the opposite kidney to determine its condition. If the extreme condition of the patient prohibits conservative measures, temporary measures less radical than ligation of the ureter, nephrectomy, or cutaneous ureterostomy would permit a conservative operation at a later date: 1, the passage of a ureteral catheter through the proximal segment of the severed ureter; 2, temporary ureterostomy, and 3, temporary nephrostomy may permit conservative surgery at a later date. In many cases, the appearance of the urinary drainage from the vagina or the abdominal incision in the early postoperative convalescence of the patient is the first evidence of ureteral injury, either unilateral or bilateral. If both ureters have been ligated or otherwise occluded, the case may be erroneously diagnosed as "suppression of urine." Failure to demonstrate urine in the bladder from 6 to 12 hours following a difficult pelvic operation renders a cystoscopic examination to determine the patency of the ureters as mandatory, for too often the patient will be treated for suppression of urine for days before the true nature of the condition is suspected. If cystoscopic examination confirms the suspicion of bilateral ureteral occlusion, an immediate unilateral nephrostomy

may prove a lifesaving measure. Temporary ureterostomy may be preferred to bilateral nephrostomy because it is technically easier to do. De-ligation of the ureter is extremely hazardous and difficult. If it is attempted by the surgeon, the aid of the urologist should be sought to push obstructed points with a large caliber catheter (9 or 11 F.) from below. This procedure would permit the surgeon to clip the ligatures quickly and recognize more than one ligated point if present. The ureteral catheters should then be passed into the renal pelvis.

In the experience of Hyman and Leiter<sup>11</sup>, in the following instances it is not advisable to reimplant a ureter into the bladder: 1, When the bladder shows considerable disease or is contracted. 2, In high ureteral injuries, where an anastomosis would be subjected to too much tension. 3, Marked thickening, dilatation and disease of the ureter. 4, When the kidney has been almost or completely destroyed. The question may arise as to whether the operation be done when the kidney is not visualized in the preoperative excretory urogram. It is well known that non-visualization does not imply absence of renal function. There are a number of reflex and acute conditions which can result in temporary failure of visualization with intravenous pyelography. One must be guided, therefore, by the general clinical as well as by the operative findings. If the lower ureter is fairly normal and the contents are not thickly purulent, one may safely transplant the ureter and follow the case subsequently with excretory urography. One can always do a nephrectomy should this become necessary. Their method is very simple; a stab opening is made in the fundus of the bladder and the ureter is pulled through this and allowed to project for about  $\frac{3}{4}$  of an inch into the lumen of the bladder. Two fine chromic catgut



sutures are used to anchor the ureter to the outside of the bladder. There should be very little suturing and minimal drainage near the anastomosis. It is most important that there be no tension in the anastomosis. The bladder should be kept at rest and empty for about 10 days. Prolonged extravescical drainage leads to periureteritis and damage to the ureter transplant. A catheter is used in the anastomosis only when the reimplanted ureter is so small that it is likely to become blocked by edema. They now have a series of 60 cases. Of 27 cases which were controlled by intravenous pyelography, for from a few months to 17 years after operation, 44.4% showed good functional results; 26% showed fair functional results, and 29.6% showed definitely poor results.

The occurrence of a vesicovaginal fistula following total hysterectomy has been discussed by Holden<sup>9</sup>, who states that the causative factors of non-obstetric fistulas are: (A) Direct injury to the bladder during operation, which is unrecognized. The importance of detecting bladder injury at the time of operation and a prompt repair by 2 to 3 layers of interrupted catgut sutures cannot be overemphasized. (B) Interference with the nerve and blood supply of the bladder, particularly in radical hysterectomy (abdominal or vaginal) for malignancy of the uterus. (C) Clamping or ligating a piece of the bladder in the closure of the vaginal vault, which later sloughs out, producing a fistula. It must be borne in mind that these fistulas, following total hysterectomy are located high up in the vaginal vault, just above or on a level with the trigone and the ureteral openings. A brief anatomic consideration will enable one to visualize the reason for the location of these fistulas. There is approximately 1 cm. of bladder wall above the trigone which is in close connection to the anterior vaginal wall.

The bladder injury usually occurs when the vagina is opened, amputated or sutured. The injury to the bladder therefore is generally near the trigone and in close proximity to the ureteral openings. After total hysterectomy, the posterior and inferior margin of the bladder is in close contact with the sutured edge of the amputated vagina, and they are both closely attached to the peritoneum. Since the absence of the uterus and cervix has eliminated the vesico-uterine fold of peritoneum; any attempt at the classical method of mobilization of the bladder in this region is not only difficult due to its inaccessibility, but is fraught with considerable danger, for the peritoneum may be easily entered. Partial colpocleisis, the Latzko operation (*ie.*, partial obliteration of the vagina), is offered as a treatment for vesicovaginal fistula. One rigid criterion exists: This operation should only be performed on fistulas resulting from *total* hysterectomy (abdominal or vaginal). In this operation one makes use of the posterior vaginal wall as a transplant over the fistulous opening. The vaginal walls being constantly in contact lend themselves readily to this procedure, placing no tension on any of the suture lines. A circular area of mucous membrane 1.5 cm. in diameter is denuded around the fistulous opening; all the vaginal mucosa up to and including the fistulous edge is removed in this area. The denuded area on the anterior vaginal wall is sutured to the denuded area on the posterior wall in 3 layers, using fine chromic catgut. Since mobilization is not needed, the necessity of inserting ureteral catheters and the hazard of injuring the ureters are practically eliminated. Furthermore, the protracted need for a postoperative indwelling catheter has not been found necessary. It should be left in for 48 hours and should then be removed and the patient should attempt to void.

With the constant flow of urine into the bladder from the ureters, it is impossible to keep the bladder dry, even with an indwelling catheter. Catheterization should be performed every 2 to 4 hours and the time gradually lengthened until the patient can void voluntarily. Overdistention of the bladder need not be feared as it cannot cause any tension on the suture line.

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# PEDIATRICS

UNDER THE CHARGE OF

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## PLASMA PROTEIN FRACTIONATION IN PEDIATRICS: A REVIEW OF ITS PRESENT STATUS

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THE plasma proteins constitute an interdissolved physiochemical mixture of awesome complexity. Cohn's recent summary describes over 25 different components, separable one from another by various analytical methods<sup>14c</sup>. The list contains 4 B<sub>1</sub>-globulins, 2  $\alpha_1$ - and 3  $\alpha_2$ - globulins, fibrinogen, antihemophilic globulin, iso-agglutinins, 2 complement components, 2 enzyme precursors (prothrombin and plasminogen), 7 serum enzymes (thrombin, amylase, lipase, esterase and others), iodoprotein, thyrotropic hormone, 2 glyco-proteins, 2 lipoproteins, bilirubin-containing  $\alpha_1$ -globulin, iron-binding protein, and 2 forms of albumin.

In addition to the precise activities denoted by the specific names borne by most of these components—fibrinogen, amylase, thyrotropic hormone, for example—the plasma proteins as a collective mass fulfill a number of highly essential functions within the metabolic and homeostatic equilibria of the body. Among these major functions may be cited: *a*, maintenance of osmotic pressure and hence

blood volume, which is primarily the responsibility of albumin because of its low molecular weight and high net negative charge at the pH of blood; *b*, transport of hormones; *c*, transport of antibodies in the  $\gamma$  globulin fraction; *d*, protection against blood loss through an intrinsic clotting mechanism; *e*, transport of nutritive elements; *f*, transport of lipids including cholesterol, phospholipids, fatty acids, fat soluble vitamins and iron<sup>37,86</sup>.

This multiplicity of functions involving the entire organism and the equilibrium of plasma proteins with those of the protoplasm, sometimes leads to distinctive alterations in composition with respect to both age and growth in a variety of normal and disease states<sup>5</sup>. Determinations of the plasma protein fractions has already been found of positive though limited help in the diagnosis of disease, as will be seen. Serial studies are of greater value, for the character of the fractions can be an index of the severity of some maladies and a guide in following their progress. Serial studies can also furnish information as to the

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efficacy of treatment and the need for its continuance. This Review briefly outlines the methods applicable to such studies, describes some of the important investigations on normal children, and surveys the practical applications to clinical pediatrics. Other more exhaustive general summaries are to be found in the articles by Edsall<sup>25</sup>, Gibson<sup>27</sup>, Gutman<sup>31</sup>, Janeway<sup>41</sup>, Loeb<sup>52</sup>, Marrack and Hoch<sup>62</sup>, Metcalf and Stare<sup>70</sup>, and Paul and associates<sup>75</sup>. The protein fractions being manufactured on a large scale for therapy, such as antihemophilic globulin, gamma globulin, comprise a broad field in themselves<sup>14a,b,15,16,56</sup> and are not dwelt upon in this Review.

**METHODS OF INVESTIGATION OF PLASMA PROTEINS. Salting Out Procedures.** By tradition, the moiety of plasma proteins which remains in solution after half saturation with ammonium sulfate is known as albumin; the precipitated portion, globulin. Globulin has been further subdivided by fractional precipitation into euglobulin, pseudoglobulin 1 and 2, and fibrinogen.

Howe's system of salt precipitation<sup>36</sup> which employs sodium sulfate has largely supplanted the ammonium sulfate method. At any given ionic strength, the salting out property of sodium sulfate is greater than ammonium sulfate. Albumin is determined from the nitrogen in the filtrate (minus the deduction of non-protein nitrogen) after precipitation with 21.5% sodium sulfate solution. The total globulin is estimated by difference. Euglobulin, pseudoglobulins 1 and 2, and fibrinogen are precipitated at lower concentrations of this solution. These fractions have been shown by electrophoresis to be far from homogeneous, and this terminology is being generally abandoned. Pseudoglobulin has been found to contain 85%  $\alpha$  globulin and 15%  $\gamma$  globulin, while euglobulin contains

more  $\beta$  globulin and  $\gamma$  globulin but less  $\alpha$  globulin. In addition, albumin as determined by salt precipitation is seriously contaminated by globulin factors which lead to particularly erroneous results when albumin is low<sup>58a</sup>. The major fractions studied are only relatively pure; they are not single entities but rather overlapping groups with similar properties<sup>95</sup>. Their characterization depends upon the method of separation. The appropriate terminology varies with the technique employed.

Serious discrepancies have been noted by many observers between the albumin-globulin ratios of normal and abnormal plasma derived from electrophoretic data and the Howe fractionation technique. Martin and Morris<sup>64</sup> have recently reported on studies designed to compare the results obtained by means of various salting-out methods with those secured by electrophoresis. They confirmed that 22% sodium sulphate, sodium sulphite, or magnesium sulphate gave data which differ significantly from the electrophoretic values. On the other hand, satisfactorily close agreement with the electrophoretic values was obtained with the precipitation methods which employ methanol or 26% sodium sulphate.

A number of simple methods for estimations of gamma globulin and other fractions has been described. Jager and Nickerson<sup>39</sup> by ammonium sulfate precipitation and Kunkel<sup>47</sup> with zinc turbidimetric methods have made gamma globulin determinations possible which check well against electrophoretic study. Kibrick and Blonstein<sup>46</sup> and Wolfson *et al.*<sup>102</sup> present modified salt precipitation techniques for blood fractionation which appear equally reliable. Serial determinations by these methods are helpful in following the course of many diseases.

Nordmann<sup>73</sup> has called attention to

stasis of blood in the vessels at the time of collection of the blood samples as an important source of error in the determinations. He found that when two blood samples were collected from the same arm, one before a tourniquet was applied and the other after it had been in place for six minutes, the total serum protein might rise from a normal level of 7.3 gm.% to 9.5 gm.%. Under the same conditions the serum albumin level rose from 4.1 gm.% to 4.7 gm.%. Thus it is essential that stasis be avoided when blood is drawn for serum protein determinations. In addition the patient should be at bed rest, since protein concentrations are higher with activity.

*Electrophoresis.* Protein molecules will migrate in an electrical field if dissolved in a suitable solvent. The speed and direction of movement is determined by the pH, the concentration of salts and the viscosity of the medium. The electrophoretic mobility is defined as the velocity in a unit electric field and varies with different protein molecular species. This principle constitutes the most reliable practical method for the determination of protein fractions at present. The ease and accuracy with which results may be read are especially advantageous.

The apparatus originated by Tiselius<sup>97</sup> projects upon a screen a pattern of curves, representing the various protein components migrating at their different speeds. The area under each curve is a measure of the concentration of each protein fraction and is expressed as gm. per 100 cc., or as percentage of the total protein. Further amplifications of the method and its interpretation and application have been adequately reviewed by Longsworth and others<sup>2,53b,55a,56,56a,97</sup>.

Electrophoresis depends upon a single property of proteins, namely, mobility in an electric field. Protein molecules of different size, shape, com-

position and biologic significance may have similar mobilities as demonstrated by ultracentrifugal study<sup>74</sup>. The patterns of alteration noted in disease are not specific but follow common trends.

The nomenclature of Tiselius for the electrophoretic patterns has been generally adopted. Usually 6 definite boundaries are observed, which in the order of their mobilities in neutral and alkaline pH are as follows: albumin,  $\alpha$  globulin,  $\alpha_2$  globulin,  $\beta$  globulin (also seen as two fractions under certain conditions), fibrinogen, and  $\gamma$  globulin. In addition, Leutschner<sup>58a</sup>, at pH 4.0, claims to have separated human albumin into 2 components:  $\alpha$  albumin (67%) and  $\beta$  albumin (33%), both of which show some alterations in disease states. Fibrinogen is very low in serum obtained from clotted blood.

*Ultracentrifugal Methods.* Ultracentrifugal studies<sup>77</sup> have a limited capacity for resolution of proteins. Their chief value lies in the estimation of molecular size of purified proteins and for evaluating the uniformity of fractions resolved by other methods. Pickels<sup>79</sup> has reviewed the theoretical and technical aspects.

*Immunochemical Methods*<sup>10,42,98</sup>. The detection of antibodies by immunologic study has been a highly specific diagnostic tool for many years. Many distinct antibodies can be detected within an electrophoretically homogeneous globulin sample. Minute quantities of abnormal proteins may be identified by this approach.

*Ethanol Precipitation.* The low temperature ethanol methods of Cohn and his associates<sup>16,72</sup> for large scale fractionation of plasma have been successfully applied to clinical study<sup>76</sup>. The components so separated have been defined in terms of electrophoretic analysis. Electrophoresis of the individual fractions obtained by

ethanol yields more detailed information than does electrophoresis of the plasma as a whole.

*Chemical.* Amino acid analyses of plasma proteins are complex and not readily applicable to routine clinical study<sup>65,91</sup>. Brand<sup>7</sup> has submitted several protein fractions to an extensive amino acid assay.

To date only two of the proteins in normal plasma have been crystallized: albumin and the iron-binding protein. Further advances necessarily await

information is in terms of salting out fractions and electrophoretic patterns, only values pertinent to these methods have been summarized.

Electrophoretic analyses are at present enjoying most widespread application to clinical problems. The absolute levels of fractions and their percentages in terms of total protein have been reported for 15 normal male adults by Dole<sup>21</sup>:

The distribution of electrophoretic components from large pools of normal

TABLE 1.—NORMAL PLASMA PROTEIN CONCENTRATION VALUES FROM BIRTH TO MATURITY\*

| Age††                             | Total Protein<br>gm./100 cc | Albumin<br>gm./100 cc | Globulin<br>gm./100 cc | Fibrinogen<br>gm./100 cc |
|-----------------------------------|-----------------------------|-----------------------|------------------------|--------------------------|
| Premature Infant                  | 4.55 ± 0.59                 | 3.55 ± 0.63           | 1.01 ± 0.45            | 0.27 ± 0.15              |
| Full term <sup>81,99</sup> Infant | 5.11 ± 0.76                 | 3.76 ± 0.43           | 1.34 ± 0.41            | 0.24 ± 0.04              |
|                                   | to                          | to                    | to                     | to                       |
| Birth to <sup>81</sup> 1 year     | 5.70 ± 0.45                 | 3.79 ± 0.33           | 1.66 ± 0.29            | 0.23 ±                   |
| 1 to 4 <sup>99</sup> years        | 6.10 ± 0.29                 | 4.97 ± 0.73           | 1.38 ± 0.68            | 0.28 ± 0.08              |
|                                   | 6.94 ± 0.47                 | 4.59 ± 0.31           | 2.03 ± 0.34            | 0.21 ± 0.06              |
|                                   |                             | to                    |                        |                          |
| 5 to 12 <sup>81</sup> years       |                             | 4.83 ± 0.30           |                        |                          |
| Under <sup>8</sup> 15 years       | 7.30 ± 0.59                 | 5.0 ± 0.78            | 2.4 ± 0.74             | 0.28 ± 0.04              |
| Adults <sup>8,99</sup>            | 7.16                        | 4.72                  | 2.49                   | with globulin            |
|                                   | 7.18 ± 0.013                | 4.59 ± 0.011          | 2.54 ± 0.13            | 0.21 ± 0.06              |
|                                   | to                          | to                    | to                     | to                       |
|                                   | 6.94 ± 0.47                 | 4.70 ± 0.32           | 2.03 ± 0.34            | —                        |

\* From Metcoff, J. and Stare, F. J. *New England J. Med.*, 236, 26, 1947.

† No significant variation with sex but some with race.

‡ The values are variable depending on the technique. Most of the reported total protein values are derived from micro-Kjeldahl and the albumin and globulin from sodium sulfate fractionation.

purification of other of the many components.

**VALUES FOR NORMALS.** When presenting data on plasma fractions, the nomenclature must conform to the method of determination. Comparisons of values under standard condition are more important than absolute figures. Values differ somewhat with variation in techniques.

In Table 1, after Metcoff and Stare<sup>70</sup>, are presented normal figures obtained by salting out with sodium sulfate. Since most of the available clinical

human plasma have been summarized by Edsall<sup>25</sup> in terms of percentage of total protein only:

**DATA RELATIVE TO CHILDREN.** The majority of normal values available for groups of infants and children have been determined by sodium sulfate precipitation. These have been referred to in Table 1. The levels therein indicated are in general agreement with earlier reports of Dodd and Minot<sup>19</sup>, who similarly observed low levels of total protein, globulin and albumin in infancy, rising with age. They further

noted that values for general clinic patients were often below normal and that these subjects more readily developed edema with infection. Somewhat higher figures were reported in the younger age groups by Rennie<sup>82</sup>. Darrow and Cary<sup>18</sup> with similar determinations found comparable results.

Rapoport *et al.*<sup>81</sup> noted low total serum proteins in premature infants with precipitable globulin fraction which was proportionately more decreased than albumin, and remained low even when albumin has attained

were higher in the mature infants. The mean readings may be tabulated as follows:

Serial weekly determinations of plasma proteins in 17 of the premature infants showed erratic fluctuations in the mean values for albumin and total protein. There was no significant increase with increasing age or development with infants fed on evaporated milk-carbohydrate formula. Sixteen other premature infants were given concentrated human serum albumin intravenously, in doses of 2 or 3 cc. of

MEAN PROTEIN CONCENTRATIONS (gm. %)

| Mean and<br>S.D.              | Albumin | Globulin Fractions |            |         |          | Fibrinogen |
|-------------------------------|---------|--------------------|------------|---------|----------|------------|
|                               |         | $\alpha_1$         | $\alpha_2$ | $\beta$ | $\gamma$ |            |
| Gm. %                         | 4.04    | 0.31               | 0.58       | 0.81    | 0.74     | 0.34       |
| S.D.                          | 0.27    | 0.051              | 0.083      | 0.126   | 0.151    | 0.059      |
| PERCENTAGES OF TOTAL PROTEINS |         |                    |            |         |          |            |
| % T.P.                        | 60.3    | 4.6                | 7.2        | 12.1    | 11.0     | 5.1        |
| S.D.                          | 2.8     | 0.7                | 1.3        | 1.9     | 2.5      | 0.6        |

FRACTIONS (as percentages of total proteins)

| Globulin |         |            |            |      |          |            |
|----------|---------|------------|------------|------|----------|------------|
|          | Albumin | $\alpha_1$ | $\alpha_2$ |      | $\gamma$ | Fibrinogen |
| Mean %   | 55.2    | 14.0       | 5.3        | 13.4 | 11.0     | 6.5        |
| S.D.     | 1.3     | 0.8        | 0.5        | 1.6  | 0.7      | 0.6        |

PROTEIN VALUES IN NEWBORN INFANTS (gm. per 100 cc.)

|   | Albumin |      | Globulin |      | Total Protein |      |
|---|---------|------|----------|------|---------------|------|
|   | Mean    | S.D. | Mean     | S.D. | Mean          | S.D. |
| Premature<br>(3 lb. 8 oz. to 5 lb. 7 oz.) | 4.3     | 0.60 | 1.60     | 0.37 | 5.6           | 0.47 |
| Mature<br>(5 lb. 8 oz. to 8 lb. 7 oz.)    | 4.8     | 0.47 | 1.75     | 0.49 | 6.4           | 0.60 |

normal levels. In premature and full term infants the most marked diminutions occurred in the fractions believed to be chiefly  $\gamma$  globulin.

McMurray and associates<sup>68</sup> have conducted an elaborate study of the albumin, globulin and total protein content of the plasma of 46 full term and 37 premature newborn infants. No significant correlation was found between the values obtained and the birth weights, but in general the values

25% solution per pound body weight (4.5 to 6.7 cc. per kg.) 2 or 3 times a week. These infants developed a steadily increasing albumin and total protein content of the plasma with an initial decrease and subsequently lower values for plasma globulin. They gained weight more rapidly, had fewer illnesses, and were discharged in a shorter time than the controls.

Longsworth, Curtis and Pembroke<sup>54</sup> studied by electrophoretic methods ten

sets of plasma taken from the placenta and mother at time of birth and found high concentrations of  $\gamma$  globulin in the newborn. Both the absolute and relative concentrations were higher than the maternal or average normal levels:

Du Pan and Moore<sup>24</sup> described serial electrophoretic studies on infants ranging from fetuses of the third month of gestation and upward to 1 year post partum. The albumin was quite low before birth and rose gradually to adult levels by 2 years. No change was noted in the  $\alpha$  and  $\beta$  globulins, both of which were low during fetal life and rose suddenly within the first 5 days of birth. This may be related to the ingestion of colostrum. A gradual rise of  $\gamma$  globulin was observed

In general, then, the albumin level is low in the first months of life, particularly in premature infants. It rises to adult levels at 6 to 12 months of age, with no significant later changes. According to Treverrow *et al.*<sup>99</sup>, the globulin falls from  $1.66 \pm 0.29$  to  $1.31 \pm 0.25$  during the first 5 weeks of life. It remains in this range until 6 months, and then a gradual rise begins to reach adult levels at 4 years. Fibrinogen is higher, with marked variation, at birth.

PROTEIN FRACTIONS IN DISEASE. A relation of disease states to high or low serum proteins has long been appreciated<sup>84</sup>. The hyperglobulinemia of pneumonia, syphilis and kala-azar and the low serum albumin of nephrosis-

#### PLACENTAL AND MATERNAL PLASMA VALUES

|                        | Fetal            | Maternal        |
|------------------------|------------------|-----------------|
| Mean total protein     | 6.18 gm. %       | 7.17 gm. %      |
| Mean $\gamma$ globulin | 15.7% (0.97 gm.) | 9.9% (0.72 gm.) |

#### PROTEIN VALUES IN NORMAL CHILDREN

| Total Protein | Albumin | Globulin Fractions |            |         | Fibrinogen |
|---------------|---------|--------------------|------------|---------|------------|
|               |         | $\alpha_1$         | $\alpha_2$ | $\beta$ | $\gamma$   |
| 7.5 gm.       | 57.7%   | 6.3%               | 10.6%      | 10.3%   | 9.7%       |
|               |         |                    |            |         | 5.2%       |

throughout fetal life, attaining a maximum at birth when it exceeded maternal levels. A steep drop occurred during the first 2 to 3 months post partum and the level remained low for 10 months.

The often reported high  $\gamma$  globulin at birth would appear to be confirmed by reports of positive cephalin-cholesterol flocculation in newborn infants, bearing no relation to icterus or the general condition<sup>80,85</sup>. However, this phenomenon could also be explained by the low albumin ordinarily exerting an inhibitory effect when in proper concentration<sup>33,71</sup>.

Routh *et al.*<sup>83</sup> report average normal figures by electrophoretic analysis on 13 normal children aged 3 to 8 years:

nephritis<sup>26</sup> have been known for many years.

The literature on alterations of plasma proteins in disease is large and uncertain. There are differences in methods and differences in normal and abnormal values even when the same methods have been used. Many diseases are not accompanied by significant variations in plasma protein fractions. Even when changes occur they are only occasionally pathognomonic, as in the distinctive pattern of multiple myeloma. Some tests, widely used in clinical pediatrics, depend upon variations in major plasma protein fractions. Thus, elevation of the sedimentation rate is believed to be related to increased plasma



fibrinogen<sup>34</sup> and  $\alpha$  globulin<sup>60</sup>. The thymol turbidity reaction depends upon elevated  $\alpha$  and  $\beta$  globulins as well as lipids, resulting in the precipitation of a globulin-thymol-lipid complex<sup>12,48,59</sup>. The colloidal gold test is influenced not only by the globulin content but also its relationship to albumin<sup>37</sup>. Cephalin-cholesterol flocculation is due primarily to a labile alteration in the albumin fraction shown electrophoretically<sup>33,71</sup>. The exact mechanisms of all these tests remain obscure.

The albumin-globulin ratio of plasma proteins as commonly used is of little value *per se* since variations may be due either to an increased globulin or diminished albumin component. An objection to determining these by precipitation methods, as stated above, is that depressed albumin levels may be obscured by globulin fractions behaving in a similar manner.

In general, electrophoretic patterns fall in albumin in wasting diseases, malnutrition, cirrhosis and nephrosis; rise in  $\gamma$  globulin in various infections, tumors, and metabolic diseases. A few common underlying mechanisms have been discovered for the hypoalbuminemia, but not for the hyperglobulinemia. The serum globulin is often high in diseases in which plasma cell reactions are prominent.

Hyperalbuminemia is seen to occur only in reference to fluid loss with hemoconcentration. Hypoalbuminemia may be due to: *a*, loss of albumin by leakage into extravascular spaces, including urine; *b*, hepatic disease, primary or secondary, with inadequate synthesis; *c*, increased protein utilization or decreased absorption.

Globulins  $\alpha_1$  and  $\alpha_2$  are closely associated with albumin. They are increased in a variety of diseases, possibly secondarily to falls in albumin.

Both  $\alpha$  and  $\beta$  globulins are carriers of lipid components<sup>53c</sup>. They appear to

be increased in several diseases, depending on abnormally large amounts of lipoids migrating with these fractions.

Gamma globulin, the component of most antibodies, is high in some subacute and chronic infections. Fibrinogen is primarily concerned with blood clotting with little fluctuation in different growth periods; high values are reported in nephrosis and low values in severe liver disease.

Stacey<sup>92</sup> reported a protein found in a series of patients with acute infections representing a "modified albumin". Like albumin, it was not precipitated by 22.2% sodium sulfate solution, but like globulin it was precipitated by methanol in water with a specific turbidity differing from Howe's albumin<sup>36</sup>. This probably represents a globulin.

The protein of disease which has been most completely studied<sup>1,60</sup> and recently crystallized<sup>67</sup> is the "C reactive protein", precipitable by the C polysaccharide of the pneumococcus. It occurs in the acute stages of a wide variety of infections including rheumatic fever, staphylococcus osteomyelitis, and is not specific with respect to the inciting agent. It is immunologically specific and completely absent from normal plasma.

*Malnutrition and Starvation.* When the body is starved the plasma proteins become depleted, just as do all the other tissues of the body. The first significant change is usually in the direction of a compensatory drop in total blood volume<sup>28,69</sup>. Only in the advanced states does the concentration of serum proteins per unit of blood volume become significantly lowered. Bieler, Ecker and Spies<sup>5a</sup> found with the electrophoretic technique that an inadequate protein intake leads to reduction of both the albumin and the globulin fractions, with proportionately greater decrease in albumin<sup>5a,88</sup>. The

gamma globulin portion of the globulin seems the most refractory to inanition diminution.

Determinations of the total protein levels have been repeatedly included in nutritional surveys of populations. It has become evident that nearly all children so surveyed have had values which fall within the normal range<sup>5,61</sup>. It is only when the state of nutrition has been severely handicapped that significant correlations become demonstrable between low protein diets and low levels of blood albumin or total protein. Gollan<sup>28</sup> noted in emaciated Italian children studied at the end of World War II, that many of them had a low albumin-globulin ratio due to a reduction in the concentration of albumin and an increase in the concentration of globulin. The albumin-globulin ratios in 8 marasmic infants ranged from 1.40 to 2.15 with an average of 1.64. Edema was not a feature, but when it became necessary to administer intravenous fluid the children developed edema very rapidly.

*Nephrosis and Nephritis.* It has been appreciated for a number of years that the total protein is greatly reduced in lipid nephrosis. The salting out technique indicated a marked diminution in albumin, often below 2.0 gm.<sup>51</sup>. As stated previously the level of albumin under circumstances was grossly inaccurate due to the inclusion of  $\alpha$  and  $\beta$  globulins, yielding higher figures.

Employing potassium phosphate fractional precipitation, Rapoport, Rubin and Chaffee<sup>51</sup> studied 11 nephrotic children. The albumin fraction was much decreased in all. The  $\alpha$  and  $\beta$  globulins precipitating at 2.0 M concentrations were somewhat above normal and the fraction precipitating earlier, between 1.6 to 2.0 M (probably  $\gamma$  globulin) was decreased, becoming normal during inactivity of the disease.

Longsworth *et al.*<sup>53,55</sup>, using electrophoretic patterns, confirmed the pres-

ence of very low serum albumin concentrations. The  $\alpha$  and  $\beta$  globulins were elevated. The patterns of urine proteins resembled closely those of normal serum. Luetscher<sup>58</sup> observed the similarity of nephrotic urine to normal serum proteins, with a predominance of albumin (67.7 to 92.0%) and an absence of fibrinogen. Three sera studied by Luetscher revealed a total protein of 3.9 to 4.2 gm. % with a marked diminution of plasma albumin (8.7 to 27.4%), which was more severe than indicated by the A/G ratio of salt precipitation. There was an elevation of  $\alpha$  globulin (15.2 to 31.7%),  $\beta$  globulin (33.0 to 41.6%), and fibrinogen (12.5 to 18.4%). The  $\alpha$  and  $\beta$  albumins observed at pH 4.0, described above, were reversed in their ratio in nephrotic serum, and urine as well; this indicates an alteration in the relative synthesis of these factors rather than differential urinary loss.

Block, Jackson, Stearns and Butsch<sup>6</sup> describe the findings in childhood nephrosis as consisting of lowering of albumin (lowest value of 0.3 gm./100 cc. blood) with increase in globulin, accompanied usually by increase in fibrinogen. High globulin values sometimes resulted in a high figure for total protein, rendering such a determination alone, without salting-out the individual protein fractions, often valueless. These results were based on both precipitation and electrophoresis determinations in 9 patients.

Routh *et al.*<sup>83</sup> studied several children in different stages of the disease by electrophoretic analysis of sera. The percentage ranges of the fractions and total protein are tabulated:

The increases in globulin were explained on 3 bases: *a*, relative to decreased albumin; *b*, less rapid loss of globulin in the urine due to its large molecular size; *c*, increased  $\alpha_2$  and  $\beta$ , as the result of augmentation

of lipoprotein fractions due to the nephrosis.

The urines were also analyzed. Albumin,  $\alpha$  and  $\beta$  globulins were always present. Alpha 2 and  $\gamma$  globulin were seen in a few. Fibrinogen was almost always absent. There was increased albumin excretion during albumin therapy. The levels in nephrosis are influenced by the course of the disease and by intravenous albumin therapy. Short period of albumin treatment for 1 to 3 days produce no change in the patterns<sup>58b,73</sup>. Albumin therapy for 2 to 6 weeks bring about moderate elevations in albumin and diminutions in globulin<sup>83</sup>.

Kunkel and Ward<sup>49</sup> have shown

Albanese, Davis, Smetak and Lein<sup>3</sup> studied the amino acid composition of urinary proteins and abdominal fluid in children with the nephrotic syndrome, and concluded that  $\alpha$ , the amino acid pattern of the urinary proteins varies with the severity of the symptoms;  $b$ , the proteins in the abdominal fluid may not simulate the proteins occurring simultaneously in the urine, and  $c$ , only in the improved stages of the disease does the albumin of the urine approximate the albumin of the blood in amino acid composition. However, since these determinations were carried out on protein mixtures no conclusions can be drawn regarding a dissimilarity of urine and blood proteins.

FRACTION PERCENTAGES OF TOTAL PROTEINS IN CHILDHOOD NEPHROSIS

| Severity                 | Total Protein<br>gm. % | Albumin | Globulin Fractions |            |         |          | Fibrinogen |
|--------------------------|------------------------|---------|--------------------|------------|---------|----------|------------|
|                          |                        |         | $\alpha_1$         | $\alpha_2$ | $\beta$ | $\gamma$ |            |
| Early (minimal edema)    | 5.6-8.2                | 21.7-   | 2.4-               | 13.3-      | 28.2-   | 6.8-     | 7.1-       |
|                          |                        | 39.1    | 4.3                | 18.3       | 38.1    | 10.4     | 10.8       |
| Moderate edema & ascites | 4.3-5.4                | 16.4-   | 4.6-               | 21.6-      | 6.2-    | 2.6-     | 6.1-       |
|                          |                        | 38.5    | 26.4               | 34.8       | 22.7    | 6.8      | 15.8       |
| Severe edema & ascites   | 3.6-6.0                | 1.4-    | 3.1-               | 25.8-      | 6.5-    | 0.5-     | 6.4-       |
|                          |                        | 30.1    | 31.5               | 61.6       | 44.2    | 15.2     | 15.9       |

hypernormal levels of esterase in nephrosis which together with the high fibrinogen has been interpreted as a general response of the liver to regenerate protein more rapidly as a result of albumin loss. Since esterase formation is not impaired, but actually accelerated, it is suggested that the defective protein synthesis in nephrosis is due not to any hepatic abnormality, but rather to lack of certain essential materials.

Luetscher<sup>58c</sup> reports low protein contents (0.1 to 0.7 gm. per 100 cc. ) in pleural and ascitic fluid of nephrotics, with electrophoretic patterns roughly resembling the plasma with somewhat higher albumin concentrations.

Recent studies by Chinard, Lawson and Van Slyke<sup>9</sup> employing immunologic methods have demonstrated that the albumin in urine and ascitic fluid is identical with that in the plasma.

*Rheumatic Fever.* No striking consistent changes have been reported in rheumatic fever by salting-out procedures. Longworth<sup>56</sup> has reported increases in the ratio of globulin to albumin to twice normal, by electrophoresis. Jager *et al.*<sup>40</sup> found elevated  $\alpha$  globulin by electrophoresis frequently in rheumatic patients, persisting after all other tests were normal. In addition 5 of 15 instances of hemolytic streptococcic pharyngitis with non-suppurative complications indicated similar

elevations of globulin, persisting for prolonged periods; other laboratory tests for rheumatic activity were negative. It is suggested that an increased  $\alpha$  globulin may be an index to persistence of the rheumatic process at less intense levels. Dole *et al.*<sup>21,22</sup> reported an early fall in serum albumin and rise in  $\alpha_1$  and  $\alpha_2$  globulin in rheumatic fever with a delayed rise in  $\gamma$  globulin generally correlated with the anti-streptolysin O titer. While the latter was of longer duration in rheumatic fever, the patterns cannot distinguish rheumatic from non-rheumatic disease. Luetscher<sup>58a</sup> reported a marked rise in  $\gamma$  globulin (33.5%),  $\beta^1$  globulin (10.0%) and fibrinogen (8.3%) in a case of acute rheumatic pancarditis, with similar findings in a second case.

Lubschez<sup>57</sup> and Wilson and Lubschez<sup>101</sup> have reported on the electrophoretic pattern in children having rheumatic fever as compared with normal children. With 30 normal children in apparent good health the relative concentration of the various components seemed in close agreement with normal values, although the individual variation was several times greater. With 27 other children in apparent health who had experienced various types of infection during a 1 to 4 month interval prior to the time the specimen was taken, elevation of the gamma component occurred in about 40% of the determinations. Illness within the month produced the greatest number of abnormalities. With 79 specimens of blood plasma or serum from 42 rheumatic subjects during apparent health, following respiratory illness, and during rheumatic fever, there occurred a prolonged elevation in the gamma component up to several months following an antecedent respiratory illness with or without the development of rheumatic fever. During acute rheumatic fever, the  $\gamma$  globulin was normal in the absence of

antecedent illness. It was concluded that elevation of the  $\gamma$  globulin component in rheumatic fever is not a function of the rheumatic process. The  $\alpha$  globulin components were usually elevated during febrile periods. No evidence was obtained in these studies that the electrophoretic response of rheumatic subjects to infection presumably streptococcal in origin differed from that of non-rheumatic individuals.

Anderson, Kunkel and McCarty<sup>4</sup> demonstrated a close parallelism between  $\gamma$  globulin changes and alterations in antistreptolysin and antistreptokinase in groups of patients with streptococcal infections. Those patients developing rheumatic fever showed further increases in these components. This response reflects a general augmentation of antibody formation in the latter but was not proposed as a basis for differentiation between individual patients.

*Still's Disease.* In 1938, Taussig<sup>96</sup> reported findings in 2 patients with Still's disease by Howe precipitation. The albumin was low in both (2.4 and 3.9) with elevation of the total globulin as high as 11.7 gm. per 100 cc. Electrophoretic studies of rheumatoid arthritis in adults<sup>21,78</sup> revealed elevation of  $\alpha$  globulin (early) and  $\gamma$  globulin (late) reverting to normal as activity subsides.

*Liver Disease.* Gray and Barron<sup>30</sup> studied the electrophoretic patterns in liver disease. Most characteristic of cirrhosis was the great increase in  $\gamma$  globulin (16 to 49%), a less remarkable rise in  $\beta$  globulin (8.0 to 28.2%) and a fall in serum albumin (31.6 to 64.5%). In addition 5 patients with common duct obstruction and jaundice had slightly decreased serum albumin and normal globulin, indicating that jaundice alone does not cause a marked rise in the latter. In acute hepatitis a low normal or moderately diminished albumin, elevated  $\gamma$  globulin and

smaller rises of  $\alpha_2$  and  $\beta$  globulins were observed. In experimental human hepatitis Havens and Williams<sup>35</sup> confirmed the above findings. The diminution in serum albumin occurred in the first week of illness and returned to normal by the fifth week, whereas the globulin fraction often remained high for three and one half months.

Kunkel and Ward<sup>49</sup> showed defective plasma esterase formation in infectious hepatitis and cirrhosis. This deficiency paralleled that of albumin. Both substances recovered only after long sustained therapy regardless of the availability of essential material for protein production.

Luetscher<sup>58a</sup> also noted a decrease in albumin (39.3%) in a cirrhotic patient with a total protein of 5.7 gm. per 100 cc.; the  $\gamma$  globulin was increased (32.0%). The reversal in  $\alpha$  and  $\beta$  albumin components previously alluded to was also present in cirrhosis. Ascitic fluid<sup>58c</sup> revealed the same relative concentrations of fractions and a total serum protein of 0.3 to 0.6 gm. %.

Paul *et al.*<sup>75</sup> reported a close similarity in electrophoretic patterns between plasma and ascitic fluid at any one time. More albumin,  $\alpha_1$  globulin and  $\gamma$  globulin occur in the fluid while plasma is richer in  $\alpha_2$  globulin,  $\beta$  globulin and fibrinogen. This suggests that selective protein enrichment of ascitic fluid is directly related to molecular size and that altered vascular permeability (as well as hypoproteinemia) may be a factor in ascitic formation. Other possible factors, reviewed by Gutman<sup>31</sup>, are increased portal pressure and the accumulation of antidiuretic substances secondary to hepatic insufficiency.

The use of concentrated serum albumin<sup>41b</sup> in cirrhosis with ascites has caused a temporary loss of edema and increased urinary output and a rise in the albumin level. This has been reported by many.

A simple turbidometric estimation of

$\gamma$  globulin described by Kunkel<sup>47</sup> has uniformly revealed elevation in liver cirrhosis.

*Tuberculosis and Sarcoid.* Seibert *et al.*<sup>88,89</sup> found a slight but significant elevation of  $\gamma$  globulin in early tuberculosis believed to represent an antibody reaction. With moderately advanced disease there was a rise of  $\alpha_2$  globulin which became more marked in the far advanced stages, along with diminution in albumin. In sarcoidosis, a great increase in total protein,  $\gamma$  globulin and  $\beta$  globulin was apparent.

Pulmonary carcinoma showed no increase in  $\gamma$  globulin but a rise in  $\alpha_2$  globulin and a diminution in total protein. These data may be helpful in distinguishing among these three sometimes confusing pictures.

Luetscher<sup>58c</sup> by electrophoretic analysis noted a moderate increase in  $\alpha$  globulin and fibrinogen in tuberculosis including an elevation of  $\gamma$  globulin in chronic disease. Tuberculous effusions had relatively high total protein concentrations with patterns resembling those of the blood.

*Lupus Erythematosus.* Hyperglobulinemia is a characteristic of this disease. Coburn and Moore<sup>41</sup> fractionated the sera from 15 of 30 patients by Howe's salt precipitation method. The albumin was depressed (median 3.1 gm. %) with an early rise in total globulin (median 3.8 gm. %) and a considerable elevation of euglobulin (1.0 to 2.1 gm %). The euglobulin rose with progression of the disease and fell with quiescence. Electrophoretic analysis of 2 sera showed an excess rise in  $\gamma$  globulin (mean 33% of the total protein) which behaved as normal globulin in the ultracentrifuge. The other globulins were normal.

*Endocrine Disease.* McCullagh and Lewis<sup>60a</sup> described the findings of electrophoretic analysis in 19 patients with Addison's disease. The total protein was within the upper normal range, with a

significant depression of albumin (43 to 55%). There was some increase in all globulin fractions but not consistently in any one.

In 8 adult patients with Cushing's syndrome<sup>66b</sup>, the albumin and  $\gamma$  globulin were depressed, and the  $\alpha$  globulin increased with normal  $\beta$  globulin and fibrinogen. All patients had low lymphocyte counts. The low  $\gamma$  globulin is in accord with Dougherty's<sup>23</sup> concept that adrenal cortical secretions cause release of  $\gamma$  globulins from lymphoid tissue; it is supposed that in Cushing's syndrome, the stores, constantly exposed to hypersecretion, are exhausted.

*Lobar Pneumonia.* Longworth *et al.*<sup>56</sup> reported a rise in  $\alpha$  globulin to double normal values as the most prominent alteration on electrophoresis in lobar pneumonia. Significant elevations of  $\beta$  globulins and fibrinogen, as well as a moderate drop in albumin were noted.

*Multiple Myeloma.* Multiple myeloma is an abnormal plasma cell tumor primarily of the bone marrow, associated with the urinary excretion of Bence-Jones protein. "Bence-Jones protein" refers to a group of proteins characterized by precipitation at 45 to 58 C. in slightly acid solution and redissolution on boiling. This disease is of interest because of its highly distinctive plasma protein fraction picture (Gutman<sup>31,32</sup>). The unique feature is the varied and anomalous serum protein picture demonstrable by both salting out and electrophoretic methods. The total protein is unusually high, often above 8.0 gm. per 100 cc. due to marked increase in the globulins. The globulin pattern is not uniform; at times it shows a rise chiefly in Howe's euglobulin (up to 9.4 gm. per 100 cc.). Pseudoglobulin I may also be up (6.5 to 6.8 gm. per 100 cc.). In other instances the euglobulin is normal and the increment is almost entirely precipitated as pseudoglobulin I. Under these circumstances, electrophoresis shows an

elevation of  $\gamma$  globulin (up to 65% of total protein) and involves little or no Bence-Jones proteinemia, showing a non-specific pattern seen in some infections. A variety of unusual precipitates and electrophoretic pictures may obtain showing components with mobilities of  $\beta$  globulin or between  $\beta$  and  $\gamma$  globulin. Some but not all of these seem to be Bence-Jones protein. Some patients show normal sera by electrophoresis, ultracentrifugation, and Howe fractionation, but these appearances do not preclude the presence of small quantities of Bence-Jones protein. The serum albumin is usually depressed but may appear normal because of Bence-Jones protein having similar solubility properties. Martin<sup>63</sup> has described an increased serum  $\gamma$  globulin component which proved heterogeneous in the ultracentrifuge and was identified with tumor material removed at post mortem.

*Miscellaneous.* A very narrow sharp peak in the globulin boundary in electrophoretic patterns was noted by Dole<sup>20</sup> in 14 of 15 normal subjects. This so-called " $\beta$  disturbance" was diminished or absent in 22 of 23 cases of poliomyelitis and 5 of Guillain-Barré syndrome<sup>45</sup>. The alterations were not related to the severity of illness and were not present in paralysis of unknown etiology or hypertrophic muscular dystrophy.

In syphilitic infants, Darrow and Cary<sup>18</sup> noted a high serum globulin (over 3.0 gm. per 100 cc.) by sodium sulfate precipitation. Electrophoretic patterns do not exhibit any characteristics for this disease and are of no assistance in differentiating between syphilitic and nonsyphilitic positive serologic tests for syphilis<sup>17</sup>.

Eight marasmic infants<sup>28</sup> suffering from malnutrition showed depressed total proteins along with an increase in total globulins. The latter were not further fractionated. Experimentally in dogs, a fall in albumin more apparent

on electrophoresis has resulted from low protein feedings. All globulins, especially  $\alpha$  globulin, were elevated<sup>103</sup>.

Two cases of congenital idiopathic hypoproteinemia have been reported in children<sup>87,94</sup> with decreases in total protein and almost complete lack of  $\gamma$  globulin by electrophoresis. In spite of the latter, a particular susceptibility to infection was not noted.

A case of Letterer-Siwe disease<sup>13</sup> revealed a low albumin (28%) and a general rise in all globulins, proportionately less in the  $\alpha_1$  fraction:  $\alpha_1$  12%,  $\alpha_2$  15%,  $\beta$  16%, and  $\gamma$  globulins 28.3%. In hyperthyroidism Lewis and McCullagh<sup>66c</sup> found low plasma albumin and increased  $\alpha$  globulins with no particular alteration in other fractions. The picture returned to normal after operation. In hypothyroidism, a diminution in both albumin and  $\alpha$  globulin with a rise in  $\beta$  globulin was seen, which returned to normal after prolonged therapy.

Recently Lepow *et al.*<sup>50</sup> have described a protein in periarteritis nodosa which precipitates spontaneously at 4 C. but differs from previously reported "cryoglobulins" in not redissolving at room temperature. Electrophoretic studies have identified it among the gamma globulins.

In 7 cases of infectious mononucleosis, Sterling<sup>93</sup> described diminutions in albumin and rises in gamma-globulin, with less constant rises in  $\alpha$ , and  $\beta$  globulin. The heterophile antibodies appeared to predominate in the gamm-globulin components.

A suggestive difference from normal in the electrophoretic behavior of hemoglobin from individuals with sickle cell anemia has recently been reported by Itano and Pauling<sup>38</sup>.

**Cerebrospinal Fluid Proteins.** Spinal fluid proteins are commonly studied by the colloidal gold test which is not a direct measure but depends upon the proportions of albumin to globulin<sup>29a,b</sup>.

Most of the globulin in cerebrospinal

fluid is Howe's pseudoglobulin, although in the first two months of life (the first 6 months in premature infants) it is euglobulin. The cerebrospinal fluid in 196 patients with various central nervous system diseases were studied by the precipitation method; while absolute levels were not pathognomonic, the euglobulin always exceeded 50% of the total globulin (averaged 78.3%) in brain abscess and was uniformly less than 50% in other conditions, including encephalitis, acute and chronic bacterial meningitis<sup>100</sup>.

In general, electrophoretic patterns correspond closely to those of blood except that  $\alpha$  globulin and fibrinogen are often absent<sup>44</sup>. In neurosyphilis the latter are present and a rise in globulin occurs.

Immunochemical techniques have also been applied to studies of cerebrospinal fluid<sup>43a</sup>. Normal values are as follows:

|               |                  |
|---------------|------------------|
| total protein | 19 to 54 mg.     |
| albumin       | 14.1 to 22.1 mg. |
| globulin      | 2.7 to 4.5 mg.   |
| A/G ratio     | 3.8 to 8.8 mg.   |
| A/G ratio     | 3.8 to 8.8       |

In 16 of 17 patients with neurosyphilis<sup>43b</sup>, a marked increase in  $\gamma$  globulins (5.6 to 116.0 mg. per 100 cc.) was noted. Ten of the 17 had normal total proteins and negative colloidal gold reactions. An increase in  $\alpha$  globulin was also found in 8 of 14 patients with multiple sclerosis. It has recently been demonstrated that serum protein fractions<sup>13</sup> are unchanged to electrophoresis for as long as 13 hours post mortem.

**Conclusion.** Alterations in plasma protein fractions often occur in disease state in childhood but of character only occasionally sufficiently unique to be pathognomonic. Nevertheless, their study, especially when repeated serially, can often yield helpful information concerning the efficacy of treatment and progress of disease. More investigations in problems of pediatric significance are needed.

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# PHYSIOLOGY

PROCEEDINGS OF THE

PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF OCTOBER 18, 1949

**The Effect of Salt Poor Human Albumin on Renal Oxygen Consumption in Man.** HAROLD G. BARKER, M.D., JOHN K. CLARK, M.D., ARCHER P. CROSLY, JR., M.D., and ALVIN J. CUMMINS, M.D. (Depts. of Surg. and Med., Med. Sch. and Hosp., Univ. of Penna.). It has been generally held that changes in renal blood flow are accompanied by like and parallel changes in oxygen consumption with an unchanged arteriovenous oxygen difference. This is the reverse of the situation in other organs. This relationship has been demonstrated by others at low blood flows but high flows have not been previously tested.

Seventy-five gm. of salt poor human albumin was given rapidly (less than 30 min.) intravenously to 5 normal human subjects as a means of elevating renal blood flow. Hemodynamic effects similar to those found by other workers were uniform for the group and consisted of elevation of renal blood flow (direct Fick), variable or unaltered glomerular filtration rate, uniformly decreased filtration fraction, depressed PAH extraction, and a fall in hematocrit. In all subjects renal A-V oxygen difference varied inversely with renal blood flow, leaving oxygen consumption unchanged—i.e., independent of renal blood flow. The increased renal blood flow seen following albumin is probably partly a result of vasodilatation in response to the increased blood volume and partly due to decreased viscosity. The decreased filtration fraction might indicate efferent arteriolar dilatation, although in the absence of a direct method for measuring glomerular filtration rate it might be argued

that albumin leads to tubular reabsorption of any test substance used for this measurement.

In one other subject we found, in agreement with Michie *et al.*, that PAH Tm remained constant in the face of an increased renal blood flow following albumin.

The findings might be consistent with a Trueta shunt were it not for the unchanging Tm which indicates that were a shunting of any kind to occur it would have to be an opening of additional channels rather than diversion of blood from cortex to medulla as Trueta has proposed.

**The Pulmonary Oxygen Diffusion Coefficient.** CHRISTIAN J. LAMBERTSEN, M.D., JOHN K. CLARK, M.D., DOMINGO M. AVIADO, JR., M.D., ROBERT G. PONTIUS, M.D., EARL S. BARKER, M.D., JOHN MOYER, M.D., and CARL F. SCHMIDT, M.D. (Depts. of Pharmacol. and Med., Univ. of Penna.). The pulmonary diffusion coefficient for oxygen ( $DO_2$ ) has been determined directly in anoxic human subjects by means of simultaneous estimation of  $O_2$  consumption and  $pO_2$  in alveolar air, mixed venous blood (obtained by right heart catheterization), and arterial blood. From the beginning it became apparent that the  $DO_2$  would be larger than expected. The resulting very small final  $\Delta pO_2$  between alveolar air and blood required minimizing the systematic errors of methods used by: *a*, refinement of the direct microtonometric determination of blood  $pO_2$  until its error was within  $\pm 2$  mm. Hg., and *b*, selection of the proper method for estimating alveolar  $pO_2$  by simul-

taneous, experimental comparison of available methods. In order to obtain reliable arterial blood samples it was necessary to minimize the lowering of  $pO_2$  caused by dilution of oxygenated pulmonary capillary blood with less well oxygenated or venous blood by having subjects breathe 8%  $O_2$  in  $N_2$ . The results indicate a  $DO_2$  of 60 and a mean alveolar-pulmonary capillary  $pO_2$  gradient of 5.4 in normal, resting subjects. These are to be compared with 30 and 10 respectively obtained by others with the indirect CO method for determining the  $DO_2$ . It is suggested that the CO values may be too low: *a*, because the behavior of a gas normal to the body may not be predictable from that of a foreign, toxic one; and, *b*, because the combination of CO with blood may not be rapid enough to justify the assumption of zero  $pCO$  in the blood during the determination of the diffusion coefficient. This is supported by the work of Roughton (*Am. J. Physiol.*, **143**, 621, 1945) who has indirectly calculated a  $DO_2$  of 60 at rest.

**New Transformation Products of Strophanthidin.** MAXIMILIAN EHRENSTEIN, Ph.D., and MARY A. WAGNER (Cox Med. Res. Inst., Univ. of Penna.). With the aim of preparing steroids structurally related to progesterone and the adrenal cortical hormones, strophanthidin has been transformed into a number of new compounds which will serve as intermediates towards this goal. In a previous publication<sup>1</sup> the conversion of strophanthidin into ethyl 3 ( $\beta$ ),5,19-trihydroxyeti-ocholanate has been described. Contrary to expectations it could not be made to undergo the Oppenauer reaction. However, when treated with Raney nickel in the presence of cyclohexanone<sup>2</sup> at  $130^\circ$ , a mixture of reac-

tion products resulted from which 4 components have been isolated in a pure form. The principal product was identified as ethyl 3-hydroxy- $\Delta^{1,3,5,10}$ -estratriene-17-carboxylate. It was saponified to 3-hydroxy- $\Delta^{1,3,5,10}$ -estratriene-17-carboxylic acid. The aromatization of ring A of the steroid nucleus under such mild conditions was unexpected. The obtained products differ structurally from estradiol only in that the secondary hydroxyl group at carbon atom 17 appears replaced by  $-COOC_2H_5$  and  $-COOH$  respectively. In spite of this structural similarity they did not produce estrus in spayed mice at a level of 10 micrograms (assay by Drs. E. A. Doisy and S. A. Thayer).

By treatment with triphenylchloromethane, ethyl 3 ( $\beta$ ),5,19-trihydroxyeti-ocholanate was transformed into ethyl 19-tritoxo-3 ( $\beta$ ),5-dihydroxyeti-ocholanate. This compound could be acetylated in position 3 and the resulting product hydrolyzed to ethyl 3 ( $\beta$ )-acetoxo-5,19 - dihydroxyeti-ocholanate. These two transformation products will be key substances in the synthesis of the steroids mentioned above.

**The Effect of Insulin and Adenosine-triphosphatase in a Reaction Coupling Oxidation with Phosphorylation.** B. D. POLIS, Ph.D., E. POLIS, L. JEDEIKIN, M. KERRIGAN, and E. KETY (Diabetic Coma Project, Phila. Gen. Hosp.). By the procedures of homogenization, differential centrifugation and washing in 0.1 M KCl solution, it is possible to prepare a yellow colored suspension of essentially mitochondria. These cellular units are capable of catalyzing the oxidation of  $\alpha$ -keto-glutaric acid with the uptake of oxygen and concomitantly of phosphorylating adenylic acid with inorganic phosphate. With the addition of a yeast hexokinase, glucose, and sodium fluoride, inorganic

1. Ehrenstein, M., and Johnson, A. R.: *J. Org. Chem.*, **11**, 823, 1946.

2. Kleiderer, E. C., and Kornfield, E. C.: *Ibid.*, **13**, 455, 1948.

phosphate is esterified to glucose-6-phosphate over the pathway of high energy phosphate systems (ATP). If the concentrations of yeast liver enzymes are so adjusted that the rate of transphosphorylation between glucose and ATP by the hexokinase system is always greater than the rate of ATP formation by way of the oxidative phosphorylation reaction catalyzed by the liver system, then any increase in the quantity of inorganic phosphate esterified must reflect a stimulation in the formation of high energy phosphate bonds by the mitochondria. This condition was satisfied by the use of less than optimal concentrations of ATP, a liver enzyme of reduced activity (aged preparation), and an excess of yeast hexokinase. The addition of insulin to this system resulted in a significantly increased rate of esterification with approximately 1 out of every 3 enzyme preparations. In a series of 166 experiments performed with 77 different liver enzyme preparations and 20 hexokinase preparations, the additions of 0.02 to 0.2 units of insulin to the test system produced a statistically significant increase ( $p < 0.001$ ) in the quantity of phosphate esterified, an increase which averaged 1.4 micromoles of phosphate (S. E. = 0.23 micromoles) over that produced in the absence of insulin. The use of a yeast hexokinase obviated the possibility of an insulin effect on the hexokinase similar to that described by Cori and coworkers. Since there was little stimulation in  $O_2$  consumption yet appreciable increase in phosphate

esterified, it was inferred that the action of the insulin in the described enzyme complex increased the efficiency of the formation of high energy phosphate bonds by an aerobic oxidation. This was made more obvious by the increased ratio of phosphate esterified to  $O_2$  consumed ( $P/O_2$ ) in the experiments with insulin as compared to those without insulin.

This effect of insulin was further investigated in an effort to increase the reproducibility and clarify the nature of the reaction observed. The additions of dinitrophenol, dodecylsulfate, sodium azide, and alloxan resulted in an inhibition of the phosphate esterified which was not released with the addition of insulin. All except sodium azide had little or no effect on the  $O_2$  consumption. The addition of a Mg activated adenosinetriphosphatase (Mg ATPase), as described by Kielley and Meyerhof, resulted in an inhibition of both  $O_2$  uptake and inorganic phosphate esterified. The addition of insulin of this Mg ATPase inhibited system, again increased the efficiency of oxidative phosphorylation. It was of interest that insulin inactivated with NaOH and heat, lowered the efficiency of phosphorylation below that of the control.

The concept of insulin acting in the interplay between enzymes forming and degrading high energy phosphate in a manner as to favor the increase in high energy phosphate has particular appeal in that it serves as a single explanation for the manifold actions reported for insulin.

# BOOK REVIEWS AND NOTICES

**CARE OF THE SURGICAL PATIENT.** By JACOB FINE, M.D., Prof. of Surgery at Beth Israel Hosp., Harvard Med. School. Pp. 544; 40 ills. Phila.: W. B. Saunders, 1949. Price, \$8.00.

THIS book, written to provide "a guide for the over-all care of the surgical patient", attempts to cover every phase of this broad problem. It deals with such varying subjects as common skin disorders, psychiatric considerations in surgery and laboratory procedures, in addition to the usual topics discussed in surgical texts. The chapters are generally short and written in a rather conversational style by men obviously qualified in their fields. It is not, however, sufficiently full or detailed to serve as a reference book or text, nor is it intended to be.

Some may question the need for such a volume for it is not the type of book one would use when confronted with a particular problem, because of its brevity in the discussion of each subject; nor could it be looked upon as a manual. This volume, however, does supply a "bird's eye view" of surgery as it is practiced in an excellent teaching center of today, and from this viewpoint it is valuable.

B. R.

**CLINICAL AUSCULTATION OF THE HEART.** By SAMUEL A. LEVINE, M.D., Clinical Prof. of Medicine, and W. PROCTOR HARVEY, M.D., Research Fellow, Harvard Medical School and Peter Bent Brigham Hospital. Pp. 327; 286 ills. Phila.: W. B. Saunders, 1949. Price, \$6.50.

AIMING "to discuss in detail the simple data pertaining to bedside auscultation that can be grasped and applied by any physician in the practice of medicine" with "comments concerning the related clinical conditions and the therapeutic implications involved . . . illustrated by occasional specific experiences and case reports," this book presents sections on heart sounds, cardiac irregularities, cardiac murmurs, and miscellaneous auscultatory findings with simultaneously-recorded phonocardiograms and electrocardiograms as the routine method of illustration.

Considerable material is provided which should stimulate the interest and answer some of the questions of physicians desiring an introduction to, or a review of, cardiac auscultation. The illustrations are copious, generally relevant, and clear. A rather full index is provided.

(718)

No great attempt is made to describe how murmurs actually sound to the ear, despite great faithfulness in depicting their phonocardiographic appearance and timing. It is frequently not made clear which murmurs or abnormalities of sounds and rhythm are easy to hear and identify and which ones require experience and practice; nor is emphasis given to situations in which the auscultatory findings are of crucial importance as compared with situations where their interest is academic. Certain important and useful tactile accompaniments of sounds and murmurs are not discussed at all: for example, thrills, the thrust of gallops, or the collapsing quality of the apex beat in mitral stenosis.

Attention should be called to descriptions of the opening snap of mitral stenosis; of "systolic gallop" (apparently considered identical with systolic click); and of the auscultatory characteristics of left and right bundle branch block, which do not make use of all the available information on these subjects. Furthermore, no mention at all is made of the uncommon but pathognomonic protodiastolic vibration associated with certain calcified pericardial scars.

Although the Authors are not obligated to provide a complete bibliography, their book not being a systematic treatise on heart sounds and murmurs either in fact or by design, it seems unfortunate that no references are provided at all, and that no quotations are made from standard or classical works which have described certain auscultatory phenomena conspicuously well. J. S.

**RAPID MICROCHEMICAL METHODS FOR BLOOD AND CSF EXAMINATIONS.** By F. RAPPAPORT, Ph.D., Laboratory Director, Hadassah Municipality Hospital, Tel-Aviv, Israel. Foreword by F. SILBERSTEIN, M.D. Pp. 404; 71 figs. New York: Grune & Stratton, 1949. Price, \$8.75.

THE Author, a well known writer in the field of laboratory procedures, adheres closely to the style of presentation found in most books on laboratory techniques. He includes a short explanatory note on the underlying principles involved and an enumeration of many changes in the various blood components in disease. Most of the methods are time proven, and many have been developed or improved upon by the Author.

It is unfortunate that he has incorporated the early Van Slyke method of CO<sub>2</sub>-combin-

ing power of the blood for the estimation of plasma alkali reserve instead of recent, more accurate procedures. The use of prothrombin per cent interchangeably with vitamin K is also objected to, as well as the way the concentration of prothrombin is calculated in the bedside technique. He employs the fallacious and undesirable calculation of prothrombin percentage based on ratio of the times of unknown and standard serums. This ratio is erroneously labeled vitamin K percentage and vitamin K content in the text and prothrombin percentage in an example.

In keeping with one of his objectives, the use of simple apparatus, sodium and potassium determinations are by iodometry instead of by the more familiar and rapid flame photometry. Although the Author's aim to avoid elaboration in apparatus appears praiseworthy, his failure to utilize photocell photometry will impair the usefulness of the book where these instruments are readily available.

The format, printing and binding are good. On the whole the manual is a good one and should serve well as a reference text for the experienced laboratory worker.

V. M.

**MEDICINE. (Volume II) DIAGNOSIS, PREVENTION, AND TREATMENT.** By A. E. CLARK-KENNEDY, M.D., Fellow of Corpus Christi College, Cambridge. Pp. 894. Balt.: Williams & Wilkins, 1949. Price, \$7.00.

THIS 2d and final volume confirms the opening paragraph of the review of the 1st volume (see this journal August, 1948). It was there stated: "This book is another brave attempt to achieve the impossible; 'It is intended to inculcate an attitude of mind. It is written to present facts which could be deduced from principles being committed to memory unnecessarily'. This highly desirable goal is unfortunately not reached by this volume."

Volume II presents 6 chapters—Clinical Diagnosis, Special Investigations, Disturbance of Function, Reactions of the Mind, and Pathological Processes. Some of it is interesting and readable; but as a whole it suffers from a certain diffuseness inherent to the Author's admitted intent to "inculcate an attitude of mind". The work is neither a textbook nor a reference book; it is unique in its field but this volume again seems to the Reviewer to fail in its difficult purpose.

The American reader will be intrigued by the many differences between the British point of view and his own. For example, on page 456 the well known British emphasis

on diagnosis by history and clinical examination without recourse to the laboratory, unless one suspects that an abnormal finding will be discovered, is apparent. O.P.

**RECENT ADVANCES IN OTO-LARYNGOLOGY.** By R. SCOTT STEVENSON, M.D., President, Section of Otology, Royal Society of Medicine. 2d ed. Pp. 395; 106 ills., 8 plates. Phila.: Blakiston, 1949. Price, \$6.00.

THIS edition strikes a useful medium between a textbook and a year-book. The Author evaluates and comments upon a wide variety of subjects selected as being of topical interest; for example—chemotherapy and antibiotics, nasal sinusitis, the tonsil problem, hearing-aids, otosclerosis, chronic middle-ear suppuration, Ménière's disease, malignant disease of the pharynx, cancer of the larynx, and bronchoscopy and esophagoscopy. This is a book that can be recommended to medically young and old alike—to general practitioners and post-graduate students of oto-laryngology as well as more seasoned specialists. N. F.

**REGIONAL ILEITIS.** By BURRILL B. CROHN, M.D., Consulting Gastroenterologist, Mt. Sinai Hospital, New York. Pp. 229; 74 figs. New York: Grune & Stratton, 1949. Price, \$5.50.

THIS monograph covers the subject of regional ileitis in detail. The author bases his statements on personal experience with 222 cases of chronic regional ileitis, 16 cases of acute regional ileitis, 38 cases of ileo-jejunitis and 22 cases of ileo-colitis, and on information gained from 257 references to the literature. The discussion of the pathology, clinical manifestations and diagnosis is excellent, leaving one with a definite feeling of understanding the nature of the disease. On the other hand the Reviewer did not feel convinced that the Author's recommendation of shortcircuiting procedures with transection of the ileum is the final answer in therapy. To date, however, such treatment seems to have given the most satisfactory results. The book is easy to read and the illustrations are excellent. It is highly recommended. W. S.

**TEXTBOOK OF GENITO-URINARY SURGERY.** Edited by H. P. WINSBURY-WHITE, M.B., Ch.B., F.R.C.S. (Edin.), F.R.C.S. (Eng.). Pp. 1046; 451 ills., many in color. Balt.: Williams & Wilkins, 1948. Price, \$20.00.

THIS excellent textbook has been written by 40 British urologists, including Winsbury-White, and covers the urinary tract and the male genital system from the surgical point

of view. The text bears witness to the wholehearted cooperation of these contributors. The subject-matter is all-inclusive and is most efficiently covered. Full discussion is given to such controversial topics as the different methods of removing prostatic obstruction.

This textbook is invaluable for medical students, residents and trained urologists alike.  
B. H.

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DERMATOLOGIE. VON J. DARIER, A. CIVATTE, and A. TZANCK. German translation by SCHWARZ of French 5th ed. Pp. 946; 269 ills. Bern, Switzerland: Hans Huber, 1949. (Imported by Grune & Stratton, New York.) Price, S. Fr. 90.

This work, a German translation of the French 5th edition of Darier's classical "*Précis de Dermatologie*" as revised by his pupil, Civatte, is claimed to represent the summation of the dermatologic knowledge of our time. Except for the addition of some discussion on penicillin in the appendix, the remainder of the content follows the original text exactly. Schwarz's product is the 3d German translation of Darier's work. The first, by J. Jadassohn, appeared in 1913, and the second, by K. H. Vohwinkel, was published in 1936. In the present translation, Schwarz has adopted the best features of her predecessors' efforts. Robert, in his foreword to this new German translation of Darier's outstanding work, believes that it will not only be of great value to students, physicians and specialists, but also is a notable contribution to practical and scientific dermatology. It is, besides, a step in the direction of furtherance of international understanding among persons of different languages.

There is little question about the value of this volume to dermatologists. The morphologic approach to the dermatoses is to a great extent supplemented by the etiologic approach given in the second part. The illustrations are usually good, but are relatively fewer than is often found in American texts. The index is not entirely satisfactory.

In spite of the reputation of the original French work by Darier, the present German translation, because of language difficulties, will find little demand among the bulk of American dermatologists. There is need for a new English translation since, as far as the Reviewer knows, none has appeared since Pollitzer's translation of the French 2d edition in 1920.  
H. B.

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PSYCHOSOMATIC MEDICINE, THE CLINICAL APPLICATION OF PSYCHOPATHOLOGY TO GENERAL MEDICAL PROBLEMS. By EDWARD

WEISS, M.D., Prof. of Clinical Medicine, Temple Univ., and O. SPURGEON ENGLISH, M.D., Prof. of Psychiatry, Temple Univ. 2d ed. Pp. 803. Phila.: W. B. Saunders, 1949. Price, \$9.50.

SINCE "all medicine is psychosomatic medicine," as the authors remind us, this book contains information which has practical interest not only for psychiatrists, but for other specialists as well as general physicians and students. Various sections in this new edition have been considerably re-organized. Moreover, a considerable amount of new material has been added in the light of new concepts and findings. There is a new chapter on psychosomatic diagnosis which includes advances in psychological testing that have been applied in psychosomatic diagnosis and prognosis. Material has been added on social work in relation to psychosomatic medicine, on orthopedics, and on physical medicine. In addition, new case material, charts, and tables have been included. One can ill afford not to be acquainted with this book. W. P.

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A TEXTBOOK OF ORAL PATHOLOGY. By THOMAS J. HILL, D.D.S., Prof. of Clinical Oral Pathology and Therapeutics, Western Reserve Univ. 4th ed. Pp. 398; 314 ills. Phila.: Lea & Febiger, 1949. Price, \$7.50.

THIS is a standard text for students of dentistry. The author has long been associated with the Institute of Pathology at Western Reserve University and in addition has had extensive experience in clinical teaching in the Dental School. The chapter on dental caries has been revised and emphasis has been placed on recent developments with reference to methods of control. The section on periodontology has been slightly modified and the terminology recommended by the Nomenclature Committee of the American Academy of Periodontology adopted. Since the author has re-used a diagram (Fig. 198) which was severely criticised in reviews of the 3d edition, he apparently does not accept the views of Gottlieb and his followers on the epithelial attachment to the tooth. The chapter on Deep Neck Infections of Dental Origin has been expanded. The use of illustrations from other texts in which anatomical structures are numbered but where the caption does not give the key to the numbers, may stimulate the student's curiosity or may be merely annoying. One illustration (Fig. 262) does not correspond with its caption. The type is more legible and the paper of better quality than in the previous edition.

P. B.

## NEW BOOKS

*Überwärmung als Heilmittel.* Von Prof. Dr. Med. HEINRICH LAMPERT. Pp. 180; 4 ills. Stuttgart: Hippokrates-verlag Marquardt & Cie., 1949. Price, 15 D.M.

"Reviews the world's literature on hyperthermia in recent decades and the good results obtained in various conditions with the author's hot baths."

*Simple Nursing.* Compiled and illustrated by WAVA McCULLOUGH, with MARJORIE MOFFIT, R.N. Pp. 238; illustrated. New York: McGraw-Hill, 1949. Price, \$2.40.

USEFULLY graphic.

*Vitamins and Hormones.* Vol. VI. Edited by ROBERT S. HARRIS, Prof. of Biochemistry of Nutrition, Mass. Inst. of Technology, and KENNETH V. THIMANN, Assoc. Prof. Plant Physiology, Harvard Univ. Pp. 435. New York: Academic Press, 1948. Price, \$7.80.

In this, the 6th volume, the following subjects by the respective authors, have been discussed: 1, The Chemistry and Biological Action of Pteroyl-glutamic Acid and Related Compounds, by Brian L. Hutchings and John H. Mowat; 2, Vitamin K, by Henrik Dam; 3, Nutritional Requirements of the Cotton Rat and Hamster by B. S. Schweigert; 4, Vitamins as Pharmacologic Agents, by Hans Molitor and Gladys A. Emerson; 5, The Assessment of Human Nutrition, by H. M. Sinclair; 6, Vitamins in Microorganisms—Distribution and Quantitative Synthesis, by J. M. Van Lanen; 7, The B Vitamins as Plant Hormones, by James Bonner and Harriet Bonner; 8, The Influence of the Adrenal Cortex on the Metabolism of Water and Electrolytes, by Edward C. Kendall. The subject and author cumulative index for volumes 1 to 5 is included in this volume.

J. J.

## NEW EDITIONS

*Textbook of Medical Treatment.* Edited by D. M. DUNLOP, M.D., Prof. of Therapeutics and Clinical Medicine, Univ. of Edinburgh, L. S. P. DAVIDSON, M.D., Physician to H. M. the King in Scotland, and J. W. McNEE, M.D., Regius Prof., Univ. of Glasgow. 5th ed. Pp. 999. Balt.: Williams & Wilkins, 1949. Price, \$8.50.

This, the 5th edition since the first appearance of the book in 1939, has been extensively revised, particularly in view of rapid recent advances. New chapters have been added on antihistamine drugs, treatment of dehydration and hypochloremia and the care of old people. The book should be useful to both students and practitioners, in spite of the fact that the terminology is that of the British pharmacopeia.

R. K.

*Shearer's Manual of Human Dissection.* Edited by CHARLES E. TOBIN, Ph.D., Assoc. Prof. of Anatomy, Univ. of Rochester. 2d ed. Pp. 286; 79 ills. Phila.: Blakiston, 1949. Price, \$4.50.

This attractively printed handbook should be of considerable value to anyone wishing independently to dissect a human body. It is not a textbook nor is it a monograph on the subject.

W. W.

*Bensley's Practical Anatomy of the Rabbit.* By E. HORNE CRAIGIE, Ph.D., Prof. of Comparative Anatomy and Neurology, Univ. of Toronto. 8th ed. Pp. 391; 124 ills., 16 plates. Phila.: Blakiston, 1949. Price, \$4.25.

This book continues to be a fine elementary laboratory text in mammalian anatomy. Detail is for the most part limited to readily demonstrable structures, although frequent correlation with microscopic anatomy and physiology is made. There are no references.

C. B.

*Psychological Medicine.* By DESMOND CURRAN, M.B., Civil Consultant in Psychological Medicine to the Royal Navy, and the late ERIC GUTTMANN, M.D. Foreword by SIR JOHN J. CONYBEARE, M.C., Physician to Guy's Hospital, London. 3d ed. Pp. 252. Balt.: Williams & Wilkins, 1949. Price, \$4.00.

In no sense a complete textbook on psychiatry, this little volume nevertheless has value for medical students as a means of introducing them to the subject. The appearance of the 3d edition is evidence of its usefulness.

*Clinical Allergy.* By LOUIS TUFT, M.D., Ass't Prof. of Clinical Medicine, Temple Univ. 2d ed. Pp. 690; 54 ills., 3 in color. Phila.: Lea & Febiger, 1949. Price, \$12.00.

This edition of a practical textbook in the field of general allergy is long overdue. The revision has been well done and is as complete as possible considering our rapidly changing knowledge, especially with regard to therapy such as the role of antihistaminic drugs and the use of antibiotics in respiratory allergic states, particularly asthma. In general, the plan of the book is unaltered. It has been streamlined and much tabulation omitted. Two new chapters have been added: Chapter X dealing with allergy to fungi and Chapter XI dealing with allergy to inhalants other than pollen and molds. These are timely and appropriately brief, as is necessary in a text of such broad coverage. Classification of the clinical manifestations of allergy is difficult and often confusing, especially to students. Table 3 is no exception. On the whole, students, general practitioners and beginners in the field, will find the book of practical value.

M. M.

*Neurology.* By ROY R. GRINKER, M.D., Director of Institute for Psychosomatic and Psychiatric Research, Michael Reese Hospital, Chicago, and PAUL C. BUEY, M.D., Prof. of Neurology and Neurological Surgery, Univ. of Illinois. 4th ed. Pp. 1145; 416 ills. Springfield, Ill.: Charles C. Thomas, 1949. Price, \$12.50.

This is a new edition of one of the best standard text-books of Neurology. It includes extensive additions and alterations, some of which relate to electroencephalography, some of which relate to electroencephalography, some of which relate to motor mechanism, new antibiotics, subarachnoid hemorrhage, arteriography, and modern techniques of pneumoencephalography. It will be a most useful book, not only to neurologists but to students and physicians who are in training in the field and to general physicians who wish to have access to pertinent literature and information.

W. P.



*Materia Medica for Nurses.* By LOIS OAKES, S.R.N., D.N., and ARNOLD BENNETT, M.P.S. 3d ed. Pp. 373. Balt.: Williams & Wilkins. 1949. Price, \$3.00.

THE call for a new edition within 2 years of the previous one testifies to the usefulness of this text.

*Les Symptômes de la Tuberculose Pulmonaire.* Par ÉDOUARD RIST, Membre de l'Académie de Médecine. 2d ed. Pp. 984; 22 figs. Paris: Masson et Cie., 1949. Price not given.

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# INDEX

## A

- Acronecrosis due to fibrin thrombi and endothelial cell thrombi, 425
- Aegerter, E., and Long, J. H., The collagen diseases, 324
- Albin, M., *see* Appelbaum, E., 260
- Albuminuria in service recruits: a laboratory study of 193 cases referred from routine medical examination, 419
- Ammonium chloride and potassium, Recent advances in parenteral fluid therapy, 567
- compounds, The toxicity of intravenous, 302
- Anemia from carcinoma of the prostate, Metastases in bone marrow and myelophthisic, 241
- pernicious, complicated by syphilis. Report of 3 cases, 179
- Anomalous right pulmonary vein entering the inferior vena cava: Two cases diagnosed during life by angiocardiology and cardiac catheterization, 31
- Anticoagulants and accelerator substance in human blood, Naturally-occurring, 70
- Aorta, Vascularization of. II. A comparative study of the aortic vascularization of several species in health and disease, 610
- Appelbaum, E., Nelson, J., and Albin, M. B., The treatment of pneumococcic meningitis with penicillin, 260
- Aramburu, T., *see* Lopez, G. C., 660
- Artane, 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride, Clinical experiences in parkinsonism with a new type of antispasmodic, 665
- Arthritic and normal subjects, Influence of physical therapy procedures on intra-articular temperature of, 543
- Atheromata, Embolization with material from, 510
- Atheromatous lesions after cauterization of the aorta followed by cholesterol administration, 603
- Atrial septal defect, The occurrence of chronic cyanosis in cases of, 516
- Auditory canal, The medicated external, 477

## B

- Bacitracin in man, The absorption, distribution, excretion and toxicity of, 439
- Barker, N. W., *see* Margulies, H., 42, 52
- Barnes, G. R., Jr., Yannet, H., and Lieberman, R., A clinical study of an institutional outbreak of acute infectious lymphocytosis, 646

- Bazett, H. C., Blood temperature and its control, 483
- Beerman, H., Drug eruptions: a survey of recent literature, 446
- Bellet, S., *see* Nadler, C. S., 308
- Block, F. B., Hysterectomy, 683
- Blood, Alterations in the serum potassium and their relation to certain constituents of the, in diabetic acidosis, 308
- cells, Diagnostic significance of "burr" red, 563
- flow, Effects of vasodilator drugs and other procedures on digital cutaneous, cardiac output, blood pressure, pulse rate, body temperature, and metabolic rate, 669
- in silicone tubes, coagulation time of, 42
- in patients receiving Dicumarol, 52
- Naturally-occurring anticoagulants and accelerator substance in human, 70
- regeneration in dogs subjected to repeated phlebotomy, A hematologic and electrophoretic study on, 58
- temperature and its control, 483
- Bock, G., *see* Meyer, L. M., 197
- Bodansky, O., Recent advances in parenteral fluid therapy with ammonium chloride and potassium, 567
- Boikan, W. S., *see* Feinberg, A. R., 298
- Bongiovanni, A. M., and Wolman, I. J., Plasma protein fractionation in pediatrics: a review of present status, 700
- Brickhouse, R. L., Lepper, M. H., Stone, T. E., and Dowling, H. F., The treatment of pneumonia and other infections with a soluble sulfonamide, gantrosan (NU-445; 3, 4-dimethyl-5-sulfanilamido-isoxazole), 133
- Brockman, L., *see* Kuskin, L., 65
- Brooks, A. M., *see* Scherf, D., 389
- Brown, H., Liver function in diabetes mellitus, 540
- "Burr" red blood cells, The diagnostic significance of, 563

## C

- Caccese, A., *see* Meyer, L. M., 197
- Calcification of the costal cartilages, Premature; its frequent association with symptoms of non-organic origin, 186
- Canelis, M., Farnell, F. J., and McGavack, T. H., Clinical experiences in parkinsonism with a new type of antispasmodic, 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride (Artane), 655
- Caplan, P. S., *see* Margolis, H. M., 121

- Carbon tetrachloride poisoning, with a report of 3 cases, Lower nephron nephrosis, 636
- Carcinoma of the prostate, Metastases in bone marrow and myelophthisic anemia from, 241
- Cardiac aneurysm, The murmurs of, 389  
 origin, Continuous peritoneal irrigation in the treatment of intractable edema of, 76  
 output, blood pressure, pulse rate, body temperature, and metabolic rate, Effects of vasodilator drugs and other procedures on blood flow, 669  
 Pericardial and, surgery, 213
- Carrión's disease with intercurrent malaria, A study of 22 cases of, 525
- Cerebral vascular accident, A study of factors affecting the prognosis of, 361
- Chemical combination of insulin with muscle (diaphragm) of normal rat, 265  
 Hormonal influences, 275
- Chloroquine, Treatment of falciparum malaria with intramuscular, 374
- Cholesterol administration, Atheromatous lesions after cauterization of the aorta followed by, 603
- Coagulation time of blood in silicone tubes, The, 42  
 in patients receiving Dicumarol, 52
- Coatney, G. R., *see* Spicknall, C. G., 374
- Collagen disease, 324
- Congenital polycystic disease of the kidney; review of the literature and data on 207 cases, 339
- Conston, A. S., *see* Greenstein, R. H., 384
- Coodley, E. L., and Molle, W. E., Metabolic study of gynecomastia associated with liver disease, 531
- Cook, A. W., and Lyons, H. A., Venous thrombo-embolic phenomena, their absence in paraplegic and tetraplegic patients, 155
- Costal cartilages, premature calcification of the; its frequent association with symptoms of non-organic origin, 186
- Cotlove, E., Spiro, D., and Vorzimer, J. J., Serial determinations of prothrombin activity in pregnancy and the puerperium, 28
- Cyanosis, The occurrence of chronic, in cases of atrial septal defect, 516
- D**
- Davis, J. O., and Shock, N. W., The effect of body position and reference level on the determination of venous and right auricular pressure, 281
- Davison, S., *see* Stats, D., 318
- DeNatale, A., *see* Schilling, F. J., 70
- Diabetes mellitus, Liver function in, 540
- Diabetic acidosis, Alterations in the serum potassium and their relation to certain constituents of the blood in, 308  
 boys, Experiences with 116 juvenile campers in a new summer camp for, 161  
 neuropathy, 408
- Diagnostic significance of "burr" red blood cells, 563
- Diazomethane poisoning: report of a fatal case with autopsy, 556
- Dicumarol, The increased hypoprothrombinemic effect of a small dose of, in congestive heart failure, 318
- Dotter, C. T., Hardisty, N. M., and Steinberg, I., Anomalous right pulmonary vein entering the inferior vena cava: Two cases diagnosed during life by angiocardiology and cardiac catheterization, 31
- Dowling, H. F., *see* Brickhouse, R. L., 133
- Drake, F. R., Narcolepsy: Brief review and report of cases, 101
- Drug eruptions: a survey of recent literature, 446
- Duodenal ulcer, Localized sealed-off perforation in recurrent, 378
- E**
- Electrocardiography, Clinical evaluation of direct writing, 37
- Electrokymography, 587
- Elias, K., *see* Zak, F. G., 510
- Ellis, H., *see* Zintel, H. A., 439
- Embolization with material from atheromata, 510
- Exophthalmic goiter in children: treatment with propylthiouracil, 493
- F**
- Fabricant, N. D., The medicated external auditory canal, 477
- Farnell, F. J., *see* Canelis, M., 655
- Farquhar, J. D., Renal studies in acute infectious (epidemic) hepatitis, 291
- Feinberg, A. R., Isaacs, J. H., and Boikan, W. S., Clinical report on the toxicity of a new mercurial diuretic (thiomerin) for subcutaneous administration, 298
- Feldman, M., Localized sealed-off perforation in recurrent duodenal ulcer, 378
- Fetterman, G. H., *see* Margolis, H. M., 121
- Field, J. B., and Rekers, P. F., Studies of the effects of flavonoids on roentgen irradiation disease. I. Protective influence of rutin in irradiated dogs, 1
- Flavonoids on roentgen irradiation disease, Studies of the effects on. I. Protective influence of rutin in irradiated dogs, 1
- Flippin, H. F., *see* Shore, P. D., 80
- Freis, E. D., *see* Moister, F. C., 549

## G

- Gabriele, A. J., and Marble, A., Experiences with 116 juvenile campers in a new summer camp for diabetic boys, 161
- Gleichman, T. K., Leder, M. M., and Zahn, D. W., Major etiological factors producing delayed resolution in pneumonia, 369
- Goiter, Exophthalmic, in children: treatment with propylthiouracil, 493
- Goiter, Pituitary gland of rats with experimental, 251
- Gold, The absorption of, from pellets of gold salts (aurothioglycolanilide) implanted subcutaneously and intramuscularly: its application in the treatment of 6 cases of rheumatoid arthritis, 121
- Gonorrhea; arthritis with penicillin, treatment of, 138
- Goodell, H., *see* Holmes, T. H., 16
- Gordon, J. E., and Kilham, L., Ten years in the epidemiology of mumps, 338
- Greenstein, R. H., and Conston, A. S., Co-existent Hodgkin's disease and Kaposi's sarcoma, 384
- Gynecomastia associated with liver disease, Metabolic study of, 531

## H

- Haley, H. B., *see* Jackson, A. S., 493
- Hardisty, N. M., *see* Dotter, C. T., 31
- Harman, J. W., *see* Tennent, E. C., 361
- Harrell, G. T., *see* Wolff, W. A., 500
- Harris, R., *see* Schlichter, J., 610
- Haugaard, N., *see* Stadie, W. C., 265, 275
- Heart failure, congestive, The increased hypoprothrombinemic effect of a small dose of Dicumarol in, 318
- Hematologic and electrophoretic study on blood regeneration in dogs subjected to repeated phlebotomy, 58
- Hendricks, E. L., *see* Karr, N. W., 302
- Henegar, G. C., and Higgins, G. M., The pituitary gland of rats with experimental goiter, 251
- Hepatitis (epidemic), Renal studies in acute infectious, 291
- Higgins, G. M., *see* Henegar, G. C., 251
- Hills, A. G., *see* Stadie, W. C., 265, 275
- Histamine, during pregnancy, administration of: apparent lack of a clinical oxytocic effect with small doses, 432
- Hodgkin's disease and Kaposi's sarcoma, Co-existent, 384
- Hollander, J. L., and Horvath, S. M., The influence of physical therapy procedures on the intra-articular temperature of normal and arthritic subjects, 543
- Hollenhorst, R. W., and Wagener, H. P., The ocular fundi in relation to operations for hypertensive cardiovascular disease, 225

- Holmes, T. H., Goodell, H., Wolf, S., and Wolff, H. G., Evidence on the genesis of certain common nasal disorders, 16
- Hormonal influences on the chemical combination of insulin with rat muscle (diaphragm), 275
- Horner, J. L., Premature calcification of the costal cartilages; its frequent association with symptoms of non-organic origin, 186
- Horton, B. T., *see* McElin, T. W., 432
- Horvath, S. M., *see* Hollander, J. L., 543
- Horwitz, O., Montgomery, H., Longaker, E. D., and Sayen, A., Effects of vasodilator drugs and other procedures on digital cutaneous blood flow, cardiac output, blood pressure, pulse rate, body temperature, and metabolic rate, 669
- Hunzicker, W. J., and Levine, H. D., Clinical evaluation of direct writing electrocardiography, 37
- Hypoglycemia, Recurrent migrainoid headaches associated with spontaneous, 209
- Hypoproteinemia, Association of with severe tropical sprue, 660
- Hypoprothrombinemic, The increased effect of a small dose of Dicumarol in congestive heart failure, 318
- Hypotension, 86
- Hysterectomy, 683

## I

- Insulin fat atrophy, 172
- Insulin with rat muscle (diaphragm), Hormonal influences on chemical combination of, 275
- Isaacs, J. H., *see* Feinberg, A. R., 298

## J

- Jackson, A. S., and Haley, H. B., Exophthalmic goiter in children: treatment with propylthiouracil, 493
- Jenkins, D. E., *see* Reid, J. J. R., 145
- Jonsson, U., *see* Rundles, R. W., 241

## K

- Kaposi's sarcoma, Co-existent Hodgkin's disease and, 384
- Karr, N. W., and Hendricks, E. L., The toxicity of intravenous ammonium compounds, 302
- Katz, L. N., *see* Schlichter, J. G., 603
- Kidney and liver function in rocky mountain spotted fever, 500
- Kidney, Congenital polycystic disease of the, 399
- Kilham, L., *see* Gordon, J. E., 338
- Kimble, S. T., *see* Stieglitz, 616
- Kuskin, L., and Brockman, L., The direction of the precordial T wave in 321 normal infants and children, 65

## L

- Lanning, M., *see* Nadler, C. S., 308  
 Lawrence, J. H., and Rosenthal, R. L., Multiple myeloma associated with polycythemia. Report of 4 cases, 149  
 Leder, M. M., *see* Gleichman, T. K., 369  
 Lepper, M. H., *see* Brickhouse, R. L., 133  
 LeRoy, G. V., *see* Zivin, S., 179  
 Levine, H. D., *see* Hunzicker, W. J., 37  
 LeWinn, E. B., Diazomethane poisoning: report of a fatal case with autopsy, 536  
 Lewis, A. E., *see* Selzer, A., 516  
 Lieberman, R., *see* Barnes, G. R., Jr., 616  
 Liver and kidney function in rocky mountain spotted fever, 500  
   disease, Metabolic study of gynecomastia associated with, 531  
   function in diabetes mellitus, 510  
   tests in general hospital practice, The value of, 191  
 Long, J. H., *see* Aegerter, E., 324  
 Longaker, E. D., *see* Horwitz, O., 669  
 Lopez, G. C., Milanes, F., Spies, T. D., Toca, R. L., Aramburu, T., and Lopez, H., The association of hypoproteinemia with severe tropical sprue, 660  
 Lopez, H., *see* Lopez, G. C., 660  
 Lymphocytosis, A clinical study of an institutional outbreak of acute infectious, 616  
 Lyons, H. A., *see* Cook, A. W., 155

## M

- Ma, R. A., *see* Zintel, H. A., 439  
 Malaria, A study of 22 cases of Carrion's disease with intercurrent malaria, 525  
 Malaria, Treatment of falciparum, with intramuscular chloroquine, 374  
 Marble, A., *see* Gabriele, A. J., 161  
 Margolis, H. M., Fetterman, G. H., and Caplan, P. S., The absorption of gold from pellets of gold salts (aurothioglucanilide) implanted subcutaneously and intramuscularly: its application in the treatment of 6 cases of rheumatoid arthritis, 121  
 Margulies, H., and Barker, N. W., The coagulation time of blood in silicone tubes, 42  
 Margulies, H., and Barker, N. W., The coagulation time of blood in silicone tubes in patients receiving Dicumarol, 52  
 Marsh, J. B., *see* Stadie, W. C., 265, 275  
 McElin, T. W., and Horton, B. T., The administration of histamine during pregnancy: apparent lack of a clinical oxytocic effect with small doses, 432  
 McGavack, T. H., *see* Canelis, M., 655  
 McGee, C., Lower nephron nephrosis: carbon tetrachloride poisoning, with a report of 3 cases, 636

- McMenemey, W. H., *see* Salt, H. B., 419  
 Menopausal syndrome, The pain reaction threshold in, 201  
 Metabolic study of gynecomastia associated with liver disease, 531  
 Metabolism of thiocyanate after prolonged administration in man, 519  
 Meyer, J., *see* Schlieter, J. G., 603  
 Meyer, L. M., Ritz, N. D., Caccese, A., Rutzy, J., Sawitsky, A., and Bock, G., Studies in pernicious anemia patients treated with liver extract and folic acid antagonists, 197  
 Migrainoid headaches, Recurrent, associated with spontaneous hypoglycemia, 209  
 Milanes, F., *see* Lopez, G. C., 660  
 Moister, F. C., and Freis, E. D., The metabolism of thiocyanate after prolonged administration in man, 519  
 Molle, W. E., *see* Coodley, E. L., 531  
 Montgomery, H., *see* Horwitz, O., 669  
 Morgan, R. H., Electrolymography, 587  
 Moses, C., The value of liver function tests in general hospital practice, 191  
 Motto, S. A., *see* Schwartz, S. O., 563  
 Multiple myeloma associated with polycythemia. Report of 4 cases, 149  
 Mumps, Ten years in the epidemiology of, 338  
 Mushett, C. W., Stern, K. G., and Silber, R. H., a hematologic and electrophoretic study on blood regeneration in dogs subjected to repeated phlebotomy, 58  
 Musser, M. J., *see* Schilling, R. F., 204, 207  
 Myeloma, Multiple, associated with polycythemia, Report of 4 cases, 149

## N

- Nadler, C. S., Bellet, S., Reinhold, J. G., and Lanning, M., Alterations in the serum potassium and their relation to certain constituents of the blood in diabetic acidosis, 308  
 Narcolepsy: Brief review and report of cases, 101  
 Nasal disorders, Evidence on the genesis of certain common, 16  
 Nelson, J., *see* Appelbaum, E., 260  
 Nephrosis, Lower nephron: carbon tetrachloride poisoning, with a report of 3 cases, 636  
 Nichols, A. C., *see* Zintel, H. A., 439

## O

- Ocular fundi in relation to operations for hypertensive cardiovascular disease, 225  
 Odel, H. M., *see* Rall, J. E., 399  
 Oestreicher, D. L., and Watson, E. M., Insulin fat atrophy, 172  
 Owen, C. R., *see* Reid, J. J. R., 145

## P

- Pagel, W., Acronecrosis due to fibrin thrombi and endothelial cell thrombi, 425
- Pain reaction threshold in the menopausal syndrome, 204
- patients with peptic ulcer, 207
- Parathyrotoxicosis; the syndrome of acute hyperparathyroidism, 624
- Parenteral fluid therapy, Recent advances in, with ammonium chloride and potassium, 567
- Parkinsonism, Clinical experiences in, with a new type of antispasmodic, 3-(1-piperidyl)-1-phenyl-1-cyclohexyl-1-propanol hydrochloride (Artane), 655
- Penicillin, treatment of gonorrheal arthritis with, 138
- pneumococcic meningitis with, 260
- Peptic ulcer, Pain reaction thresholds in patients with, 207
- Pericardial and cardiac surgery, 213
- Peritoneal irrigation, Continuous, in the treatment of intractable edema of cardiac origin, 76
- Pernicious anemia complicated by syphilis. Report of 3 cases, 179
- patients treated with liver extract and folic acid antagonists, Studies in, 197
- Physical therapy procedures, The influence of, on intra-articular temperature of normal and arthritic subjects, 543
- Pituitary gland of rats with experimental goiter, 251
- Plasma protein fractionation in pediatrics: a review of present status, 700
- Pneumococcic meningitis, Treatment of with penicillin, 260
- Pneumonia and other infections, The treatment of, with a soluble sulfonamide, gantrosan (NU-445; 3,4-dimethyl-5-sulfaniamido-isoxazole), 133
- Pneumonia, Major etiological factors producing delayed resolution in, 369
- Studies of a sulfadiazine-sulfamerazine combination with special reference to treatment of, 80
- Polycythemia, Multiple myeloma associated with, 149
- Potassium and ammonium chloride, Recent advances in parenteral fluid therapy, 567
- Premenstrual intoxication, 616
- Prostate, Metastases in bone marrow and myelophthisic anemia from carcinoma of the, 241
- Pulmonary vein, Anomalous right, entering the inferior vena cava: Two cases diagnosed during life by angiocardiography and cardiac catheterization, 31

## R

- Rall, J. E., and Odel, H. M., Congenital polycystic disease of the kidney; review of the literature and data on 207 cases, 399
- Reid, J. J. R., Jenkins, D. E., and Owen, C. R., Inefficacy of prophylactic streptomycin in an outbreak of salmonella gastroenteritis, 145
- Reinhold, J. G., *see* Nadler, C. S., 308
- Reinhold, J. G., *see* Shore, P. D., 80
- Rekers, P. F., *see* Field, J. B., 1
- Renal studies in acute infectious (epidemic) hepatitis, 291
- Reviews (authors' initials in parentheses):-
- Adams, L. A., Comparative Anatomy (H. R.), 240
- Bast, T. H., and Anson, B. J., The Temporal Bone and the Ear (W. W.), 237
- Bettley, F. R., Skin Diseases in General Practice (H. B.), 598
- Birkeland, J., Microbiology and Man (H. M.), 240
- Bloom, W., Histopathology of Irradiation from External and Internal Sources (W. S.), 238
- Brandt, W., Lehrbuch der Embryologie (S. W.), 238
- Brodsky, R. H., Atlas of Oral and Facial Lesions (and Color Film Library) (L. B.), 119
- Burch, G. E., and Winsor, T., A Primer of Electrocardiography (E. K.), 239
- Burstein, C. L., Fundamental Considerations in Anesthesia (J. E.), 601
- Carter, H. E. (Ed.), Biochemical Preparations, Vol. I (D. W.), 120
- Chang, K., *et al.*, Studies on Hookworm Disease in Szechwan Province, West China (H. R.), 600
- Clark-Kennedy, A. E., Medicine, Vol. 2 (O. P.), 719
- Coburn, A. F., and Young, D. C., The Epidemiology of Hemolytic Streptococcus (H. M.), 360
- Conn, H. F. (Ed.), Current Therapy, 1949 (H. H.), 119
- Cournand, A., Baldwin, J. S., and Himmelstein, A., Cardiac Catheterization in Congenital Heart Disease (R. K.), 236
- Craigie, E. H., Bensley's Practical Anatomy of the Rabbit (C. B.), 721
- Crohn, B. B., Regional Ileitis (W. S.), 719
- Darier, J., Civatte, A., and Tzanck, A., Dermatology (H. B.), 720
- Davison, W. C., The Complete Pediatrician (I. W.), 360
- Dunlop, D. M., Davidson, L. S. P., and McNee, J. W., Textbook of Medical Treatment (R. K.), 721
- Evans, W., Cardiology (H. F.), 599
- Fieser, L. F., and Fieser, M., Natural Products related to Phenanthrene (J. H.; M. S.), 236
- Fine, J., Care of the Surgical Patient (B. R.), 718
- Florkin, M., Biochemical Evolution (H. V.), 236
- Grinker, R. R., Neurology (W. P.), 721
- Harris, R. S., and Thimann, K. V., Vitamins and Hormones, Vol. 6 (J. J.), 721
- Hayes, E. W., *et al.* (Eds.), The Fundamentals of Pulmonary Tuberculosis and its Complications (E. L.), 598
- Henderson, I. F. and W. D., A Dictionary of Scientific Terms (E. K.), 360
- Hill, F. C., Operative Surgery (C. K.), 237
- Hill, T. J., A Textbook of Oral Pathology (P. B.), 720

Hollander, J. L. (Ed.), *Comroe's Arthritis and Allied Conditions* (P. C.), 601  
 Kapferer, R., *Hippokrates-Fibel* (E. K.), 600  
 Kleiner, J. S., *Human Biochemistry* (D. W.), 120  
 Krantz, J. C., *The Pharmacological Principles of Medical Practice* (I. S.), 236  
 Leicester, H. M., *Biochemistry of the Teeth* (P. B.), 119  
 Levine, S. A., and Harvey, W. P., *Clinical Auscultation of the Heart* (J. S.), 718  
 Lichtman, S. S., *Diseases of the Liver, Gall-bladder and Bile Ducts* (W. S.), 600  
 Lind, L. R., *The epitome of Andreas Vesalius* (E. K.), 482  
 Maximow, A. A., *A Textbook of Histology* (C. B.), 598  
 Mayo Clinic Diet Manual (G. R.), 120  
 McLester, J. S., *Nutrition and Diet in Health and Disease* (H. R.), 602  
 Medical Clinics of North America, New York Number, May, 1949 (C. C.), 602  
 Mitscherlich, A., and Mielke, F., *Doctors of Infamy* (E. K.), 239  
 Mottram, V. H., and Graham, G., *Hutchison's Food and the Principles of Dietetics* (I. W.), 599  
 Ogilvie, Sir H. (Ed.), *Early Recognition of Disease* (O. P.), 236  
 Orley, A., *Neuroradiology* (E. P.), 119  
 Orr, H. W., *On the Contributions of Hugh Owen Thomas, Sir Robert Jones, and John Riddell to Modern Orthopedic Surgery* (P. C.), 235  
 Pepper, O. H. P., *Medical Etymology* (E. K.), 600  
 Pincus, G., and Thimann, K. V. (Eds.), *The Hormones*, Vol. I (E. R.), 238  
 Rappaport, F., *Rapid Microchemical Methods for Blood and CSF Examinations* (V. M.), 719  
 Rivers, T. M. (Ed.), *Viral and Rickettsial Infections of Man* (W. S.), 235  
 Rosenzweig, S., *Psychodiagnosis* (W. P.), 601  
 Sanchis-Olmos, V., *Skeletal Tuberculosis* (C. B.), 360  
 Sicher, H., *Oral Anatomy* (W. W.), 240  
 Simmons, J. S., and Kinsey, I. M., *Public Health in the World Today* (E. K.), 235  
 Sommers, I. G., *Histology and Histopathology of the Eye and its Adnexa* (F. A.), 237  
 Speed, J. S., and Smith, H., *Campbell's Operative Orthopedics* (P. C.), 238  
 Stevenson, R., Scott, *Recent Advances in Otolaryngology* (N. F.), 719  
 Stitt, E. R., Clough, P. W., and Branham, S. E., *Practical Bacteriology, Hematology and Parasitology* (A. R.), 120  
 Thomas, E. W., *Syphilis: Its Course and Management* (H. B.), 599  
 Tobin, C. E., *Shearer's Manual of Human Dissection* (W. W.), 721  
 Tuft, L., *Clinical Allergy* (M. M.), 721  
 Van Ingen, P., *The New York Academy of Medicine, Its First Hundred Years* (E. K.), 482  
 Weiss, E., *Psychosomatic Medicine* (W. P.), 720  
 Winsbury-White, H. P., *Textbook of Genitourinary Surgery* (B. H.), 720  
 Woglom, W. H., *Discoverers for Medicine* (I. Z.), 235  
 Wold, K. C., *Mr. President—How is Your Health?* (E. K.), 120  
 Yater, W. M., *Fundamentals of Internal Medicine* (H. Z.), 602  
 Zimmer, H. R., *Hindu Medicine* (E. K.), 598

Rheumatoid arthritis, The absorption of gold from pellets of gold salts (aurothioglycolanilide) implanted subcutaneously and intramuscularly: its application in the treatment of, 121  
 Ricketts, W. E., *A study of 22 cases of Carrion's disease with intercurrent malaria*, 525  
 Ritz, N. D., *see* Meyer, L. M., 197  
 Rocky mountain spotted fever, liver and kidney function in, 500  
 Roentgen irradiation disease, Studies of the effects of flavonoids on. I. Protective influence of rutin in irradiated dogs, 1  
 Rosenthal, R. L., *see* Lawrence, J. H., 149  
 Rundles, R. W., and Jonsson, U., *Metastases in bone marrow and myelophthisic anemia from carcinoma of the prostate*, 241  
 Rutin in irradiated dogs, I. Protective influence of. Studies of the effects of flavonoids on roentgen irradiation disease, 1  
 Rutzky, J., *see* Meyer, L. M., 197

## S

Salmonella gastroenteritis, Inefficacy of prophylactic streptomycin in an outbreak of, 145  
 Salt, H. B., and McMenemey, W. H., *Albuminuria in service recruits: a laboratory study of 193 cases referred from routine medical examination*, 419  
 Sawitsky, A., *see* Meyer, L. M., 197  
 Sayen, A., *see* Horwitz, O., 669  
 Scherf, D., and Brooks, A. M., *The murmurs of cardiac aneurysm*, 389  
 Schilling, F. J., and DeNatale, A., *Naturally-occurring anticoagulants and accelerator substance in human blood*, 70  
 Schilling, R. F., and Musser, M. J., *The pain reaction threshold in the menopausal syndrome*, 204  
 Schilling, R. F., and Musser, M. J., *Pain reaction thresholds in patients with peptic ulcer*, 207  
 Schlichter, J., and Harris, R., *The vascularization of the aorta. II. A comparative study of the aortic vascularization of several species in health and disease*, 610  
 Schlichter, J. G., Katz, L. N., and Meyer, J., *The occurrence of atheromatous lesions after cauterization of the aorta followed by cholesterol administration*, 603  
 Schneierson, S. J., *Continuous peritoneal irrigation in the treatment of intractable edema of cardiac origin*, 76  
 Schwartz, S. O., and Motto, S. A., *The diagnostic significance of "burr" red blood cells*, 563  
 Selzer, A., and Lewis, A. E., *The occurrence of chronic cyanosis in cases of atrial septal defect*, 516

- Serial determinations of prothrombin activity in pregnancy and the puerperium, 28
- Shock, N. W., *see* Davis, J. O., 281
- Shore, P. D., Flippin, H. F., and Reinhold, J. G., Studies of a sulfadiazine-sulfamerazine combination with special reference to treatment of pneumonia, 80
- Silber, R. H., *see* Mushett, C. W., 58
- Smathers, H. M., Pericardial and cardiac surgery, 213
- Spicknall, C. G., Terry, L. L., and Coatney, G. R., The treatment of falciparum malaria with intramuscular chloroquine, 374
- Spies, T. D., *see* Lopez, G. C., 660
- Spiro, D., *see* Cotlove, E., 28
- Spitzer, N., and Steinbrocker, O., The treatment of gonorrheal arthritis with penicillin, 138
- Sprue, Association of hypoproteinemia with severe tropical, 660
- Stadie, W. C., Haugaard, N., Marsh, J. B., and Hills, A. G., The chemical combination of insulin with muscle (diaphragm) of normal rat, 265
- Stadie, W. C., Haugaard, N., Hills, A. G., and Marsh, J. B., Hormonal influences on the chemical combination of insulin with rat muscle (diaphragm), 275
- Stats, D., and Davison, S., The increased hypoprothrombinemic effect of a small dose of dicumarol in congestive heart failure, 318
- Steinberg, I., *see* Dotter, C. T., 31
- Steinbrocker, O., *see* Spitzer, N., 138
- Stern, K. G., *see* Mushett, C. W., 58
- Stieglitz, E. J., and Kimble, S. T., Premenstrual intoxication, 616
- Stone, T. E., *see* Brickhouse, R. L., 133
- Streptomycin, Inefficacy of prophylactic, in an outbreak of salmonella gastroenteritis, 145
- Sulfadiazine-sulfamerazine combination, Studies of a, with special reference to treatment of pneumonia, 80
- Sulfonamide, The treatment of pneumonia and other infections with a soluble, gantrosan (NU-445; 3,4-dimethyl-5-sulfanilamido-isoxazole), 133
- Syphilis, Pernicious anemia complicated by. Report of 3 cases, 179
- T**
- Tennent, E. C., and Harman, J. W., A study of factors affecting the prognosis of cerebral vascular accident, 361
- Terry, L. L., *see* Spicknall, C. G., 374
- Thiocyanate, Metabolism of after prolonged administration in man, 549
- Thiomerin, Toxicity of a new mercurial diuretic for subcutaneous administration, Clinical report on, 298
- Threefoot, S. A., Hypotension, 86
- Toca, R. L., *see* Lopez, G. C., 660
- Toxicity of bacitracin, absorption, distribution, excretion and, in man, 439
- intravenous ammonium compounds, 302
- a new mercurial diuretic (thiomerin) for subcutaneous administration, Clinical report on, 298
- Treatment of falciparum malaria with intramuscular chloroquine, 374
- gonorrheal arthritis with penicillin, 138
- intractable edema of cardiac origin, Continuous peritoneal irrigation in the, 76
- pneumococcic meningitis with penicillin, 260
- pneumonia and other infections with a soluble sulfonamide, gantrosan (NU-445; 3,4-dimethyl-5-sulfanilamido-isoxazole), 133
- pneumonia, Studies of a sulfadiazine-sulfamerazine compound special reference to, 80
- six cases of rheumatoid arthritis, The absorption of gold from pellets of gold salts (aurothioglycolanilide) implanted subcutaneously and intramuscularly, 121
- with propylthiouracil, Exophthalmic goiter in children, 493
- T wave, The direction of the precordial, in 321 normal infants and children, 65
- U**
- Ulcer, Localized sealed-off perforation in recurrent duodenal, 378
- V**
- Vascular accident, A study of factors affecting the prognosis of cerebral, 361
- Vascularization of the aorta. II. A comparative study of the aortic vascularization of several species in health and disease, 610
- Vasodilator drugs and other procedures, Effects of, on digital cutaneous blood flow, cardiac output, blood pressure, pulse rate, body temperature, and metabolic rate, 669
- Venous and right auricular pressure, The effect of body position and reference level on the determination of, 281
- thrombo-embolic phenomena, their absence in paraplegic and tetraplegic patients, 155
- Vorzimer, J. J. *see* Cotlove, E., 28
- W**
- Wagener, H. P., *see* Hollenhorst, R. W., 225
- Waife, S. O., Parathyrotoxicosis: the syndrome of acute hyperparathyroidism, 624



- Watson, E. M., *see* Oestreicher, D. L., 172  
 Wilkinson, C. F., Jr., Recurrent migrainoid  
 headaches associated with spontaneous  
 hypoglycemia, 209  
 Wolf, S., *see* Holmes, T. H., 16  
 Wolff, H. G., *see* Holmes, T. H., 16  
 Wolff, W. A., and Harrell, G. T., Liver and  
 kidney function in rocky mountain spotted  
 fever, 500  
 Wolman, I. J., *see* Bongiovanni, A. M., 700

## Y

- Yannet, H., *see* Barnes, G. R., Jr., 616

## Z

- Zahn, D. W., *see* Gleichman, T. K., 369  
 Zak, F. G., and Elias, K., Embolization wi  
 material from atheromata, 510  
 Zins, E. I., Diabetic nephropathy, 408  
 Zintel, H. A., Ma, R. A., Nicholas, A. C.  
 and Ellis, H., The absorption, distribution,  
 excretion and toxicity of bacitracin  
 man, 439  
 Zivin, S., and LeRoy, G. V., Perniciou  
 anemia complicated by syphilis. Report o  
 3 cases, 179

